Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

DECEMBER, 1956 Volume 49 Number 12

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DECEMBER 1956

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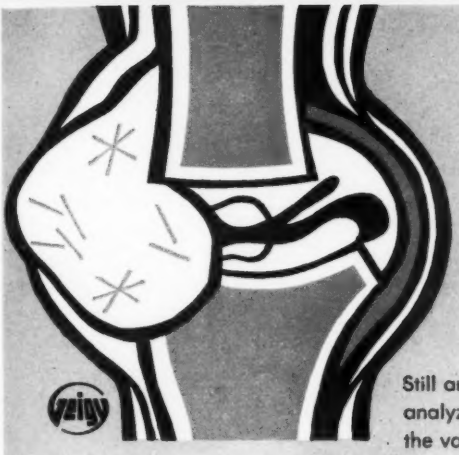

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1. Denko, C. W.; Ruml, D., and Bergenstal, D. M.: Am. Pract. & Digest Treat. 6:1865, 1955.
2. Holbrook, W. P.: M. Clin. North America 39:405, 1955.
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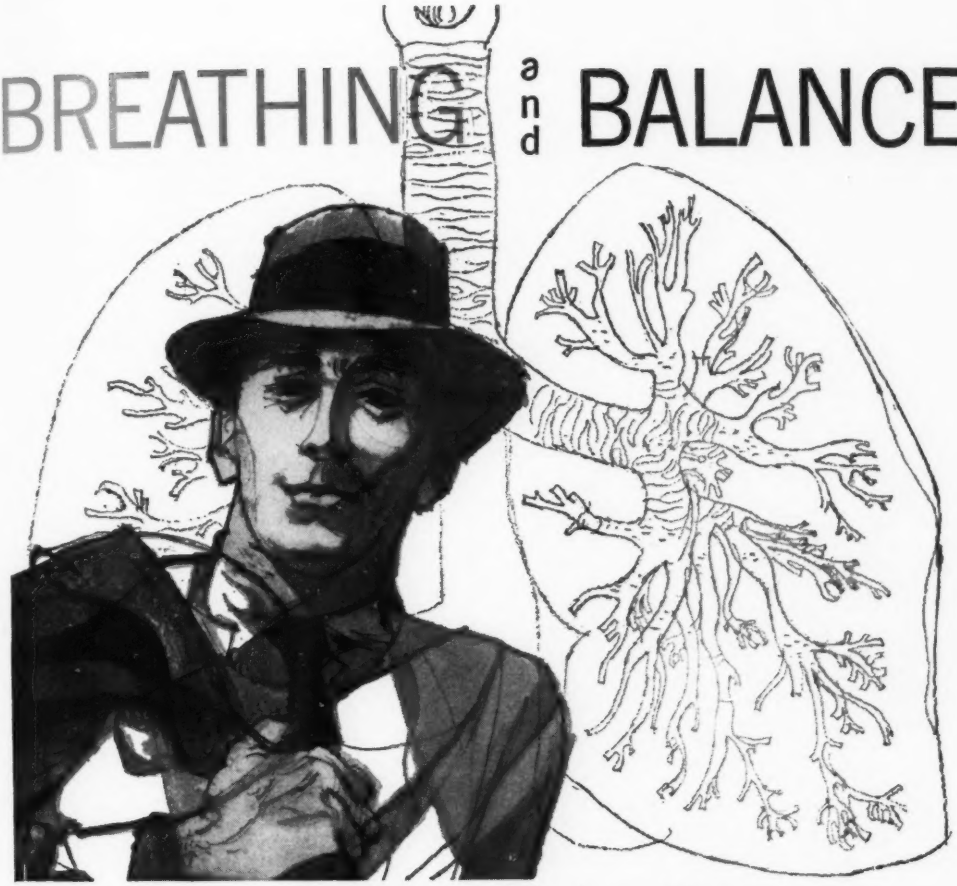

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*Schwartz, E.: New York J. Med. 56:570, 1956.

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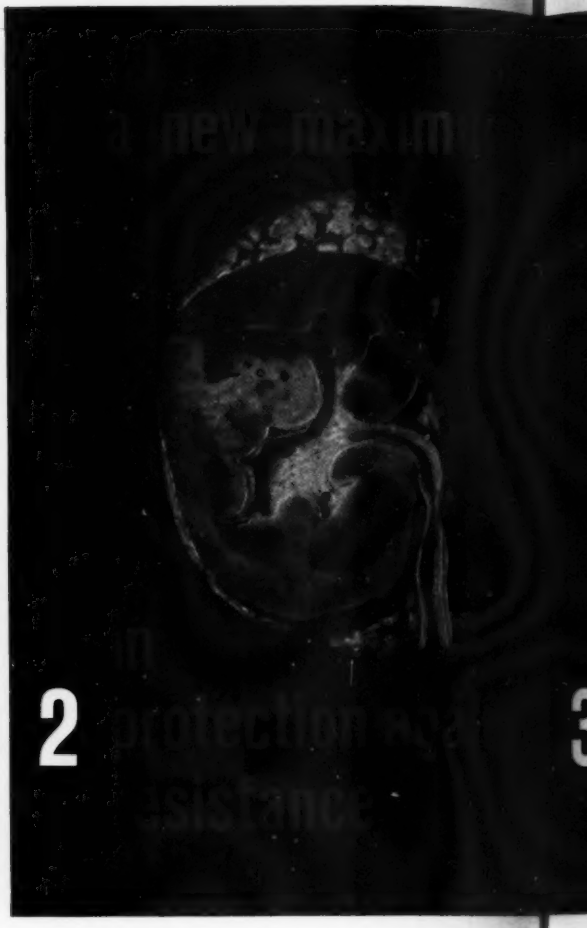

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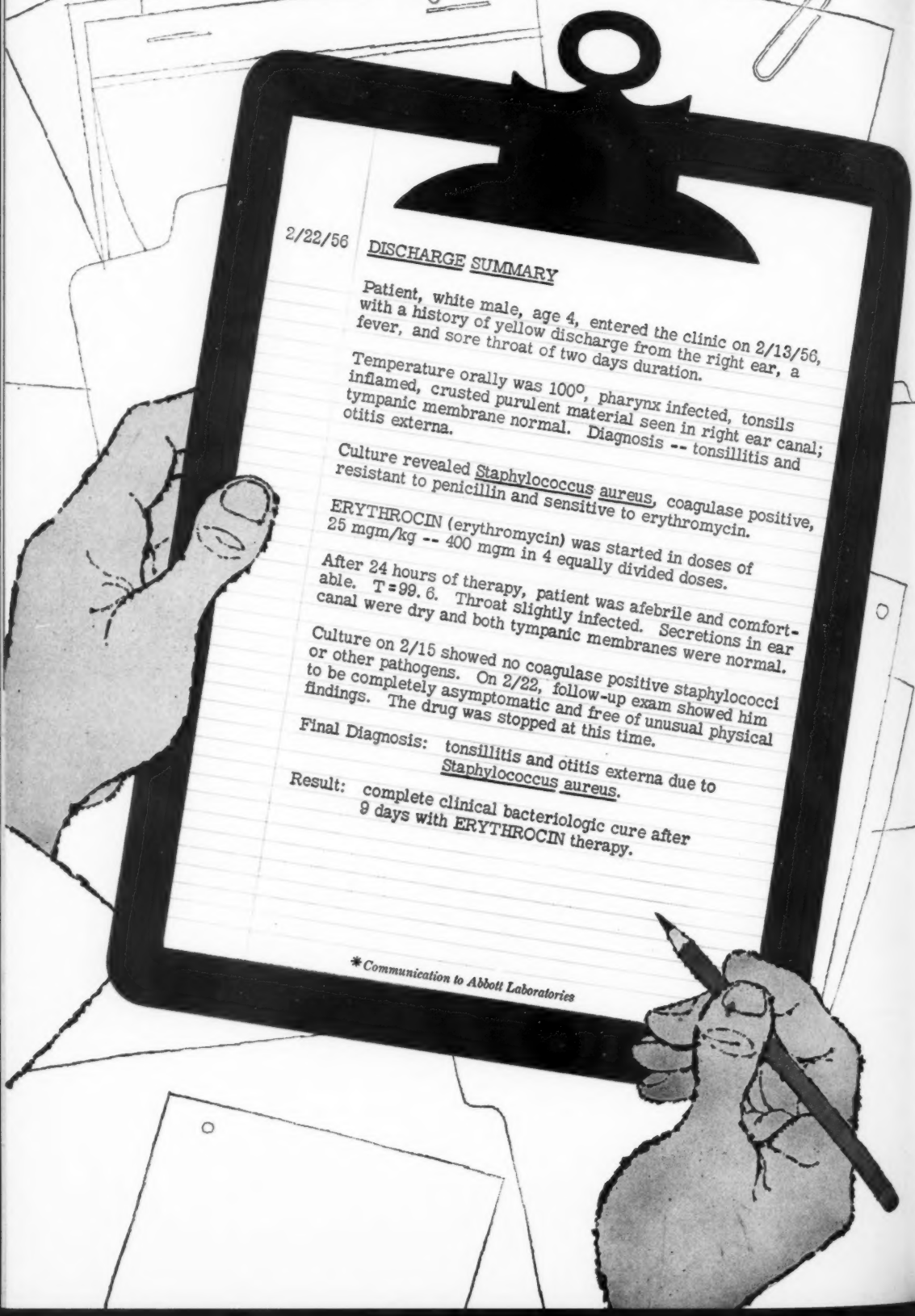

2/22/56 DISCHARGE SUMMARY

Patient, white male, age 4, entered the clinic on 2/13/56, with a history of yellow discharge from the right ear, a fever, and sore throat of two days duration.

Temperature orally was 100°, pharynx infected, tonsils inflamed, crusted purulent material seen in right ear canal; tympanic membrane normal. Diagnosis -- tonsillitis and otitis externa.

Culture revealed Staphylococcus aureus, coagulase positive, resistant to penicillin and sensitive to erythromycin.

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Final Diagnosis: tonsillitis and otitis externa due to Staphylococcus aureus.

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*Communication to Abbott Laboratories

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1. Herrell, W. E., Erythromycin, Antibiotics Monographs, No. 1, p. 29, New York, Medical Encyclopedia, Inc., 1955.
Idem p. 30.

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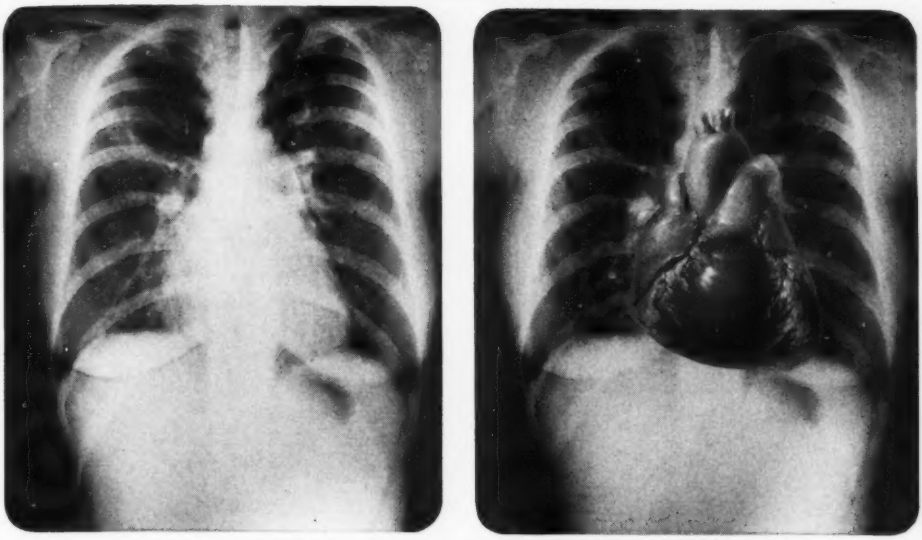

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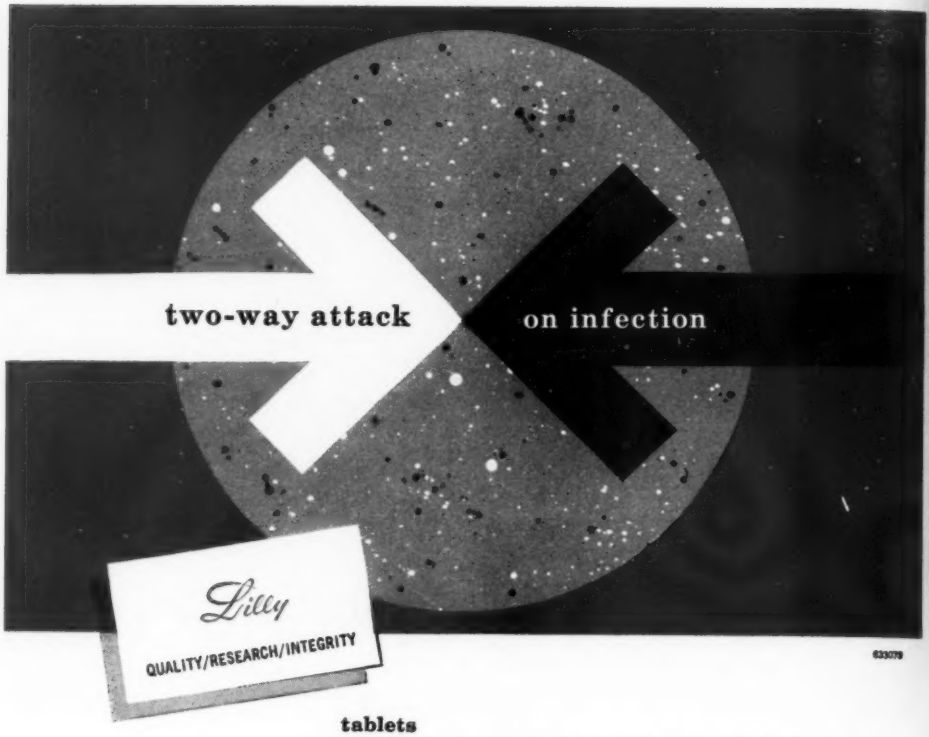
*EHRLICH, J.C.: ARIZONA MED. 12:239 (JUNE) 1955. BIBLIOGRAPHY FURNISHED ON REQUEST



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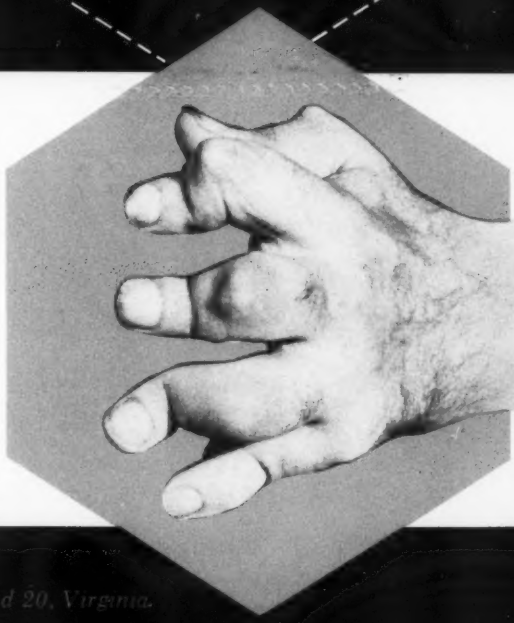

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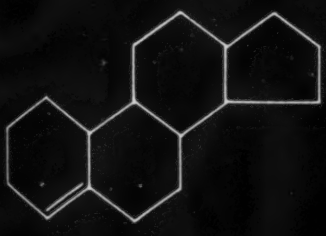

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***Barden, F. W. et al.: Journal of the Maine Med. Assoc. 46:99, 1955.**
Cass, L. J. et al.: Journal-Lancet 76:42, 1956.
Smith, R. T.: Journal-Lancet 70:192, 1950.

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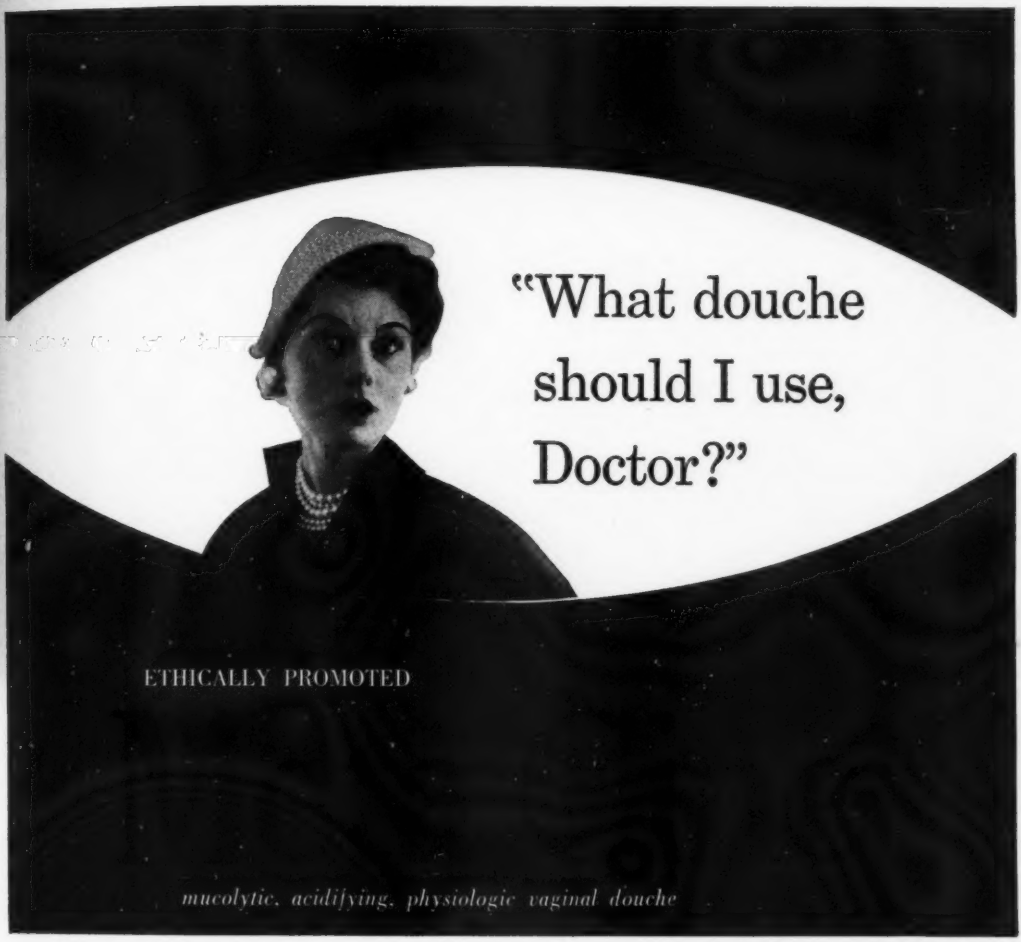

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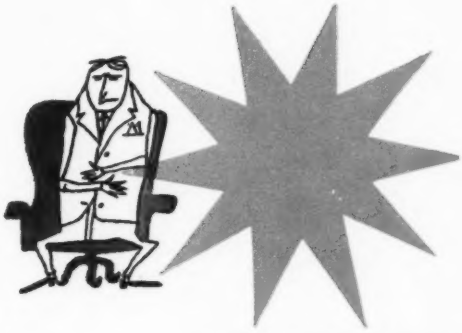

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- Safe . . . nonirritating . . . nonsensitizing.
- Cherry flavored . . . pleasant and easy to take.
- Xylocaine Viscous has proved valuable in the "dumping" syndrome, hiccup, pyloric spasm caused by peptic ulcer, stomatitis, pharyngitis, esophagitis, acute cardiospasm, pylorospasm in infants, severe vomiting of pregnancy, esophagoscopy, gastroscopy, gastric intubation and gastric lavage.
- Contains 2% Xylocaine Hydrochloride in an aqueous solution adjusted to a suitable consistency with carboxymethylcellulose. Cherry flavored for palatability.

Supplied: In bottles of 100 and 450 cc.
Average Dosage: One tablespoonful, administered orally.
Additional information available upon request

ASTRA

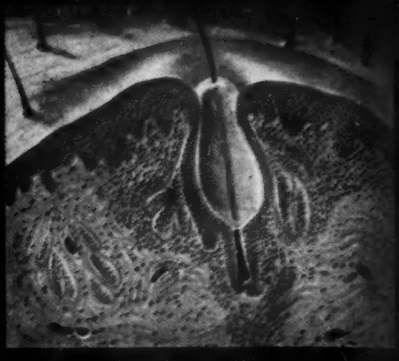
Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.

*U.S. Patent No. 2,441,498

a new maximum

1 in therapeutic effectiveness

a new maximum



2 protection against resistance

3

NEW Sigma

to meet the req

OLEANDOMYCIN TETRACYCLINE

World
Devel

a new maximum

in
3 safety
and toleration

a new certainty
in antibiotic therapy...
particularly for the 90% of
patients treated
at home or in the office...

as in the treatment of soft
tissue infections

The new synergistic formulation of tetracycline with oleandomycin (Matromycin®) brings to antibiotic therapy a new extended antimicrobial spectrum which includes even "resistant" staphylococci, while it provides protection against the emergence of *new* resistant strains. Indicated in soft tissue infections such as cellulitis, furuncles, wound infections; also as an adjunct to surgical therapy of carbuncle, lung abscess.

Supplied: Capsules, 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.).

the requirements of antibiotic therapy today

namycin*

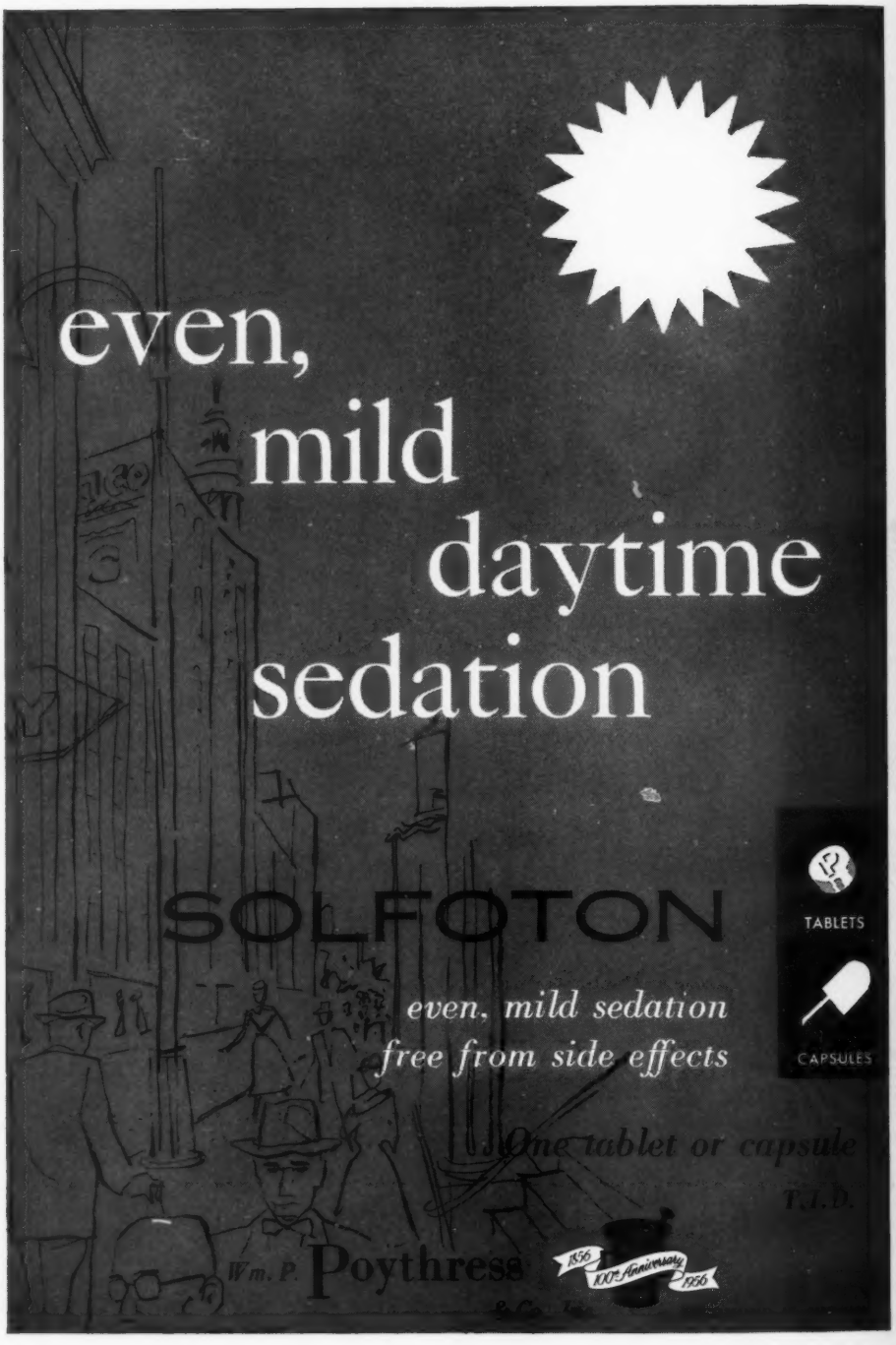
synergistically strengthened multi-spectrum antibiotic formulation

World Leader in Antibiotic Development and Production

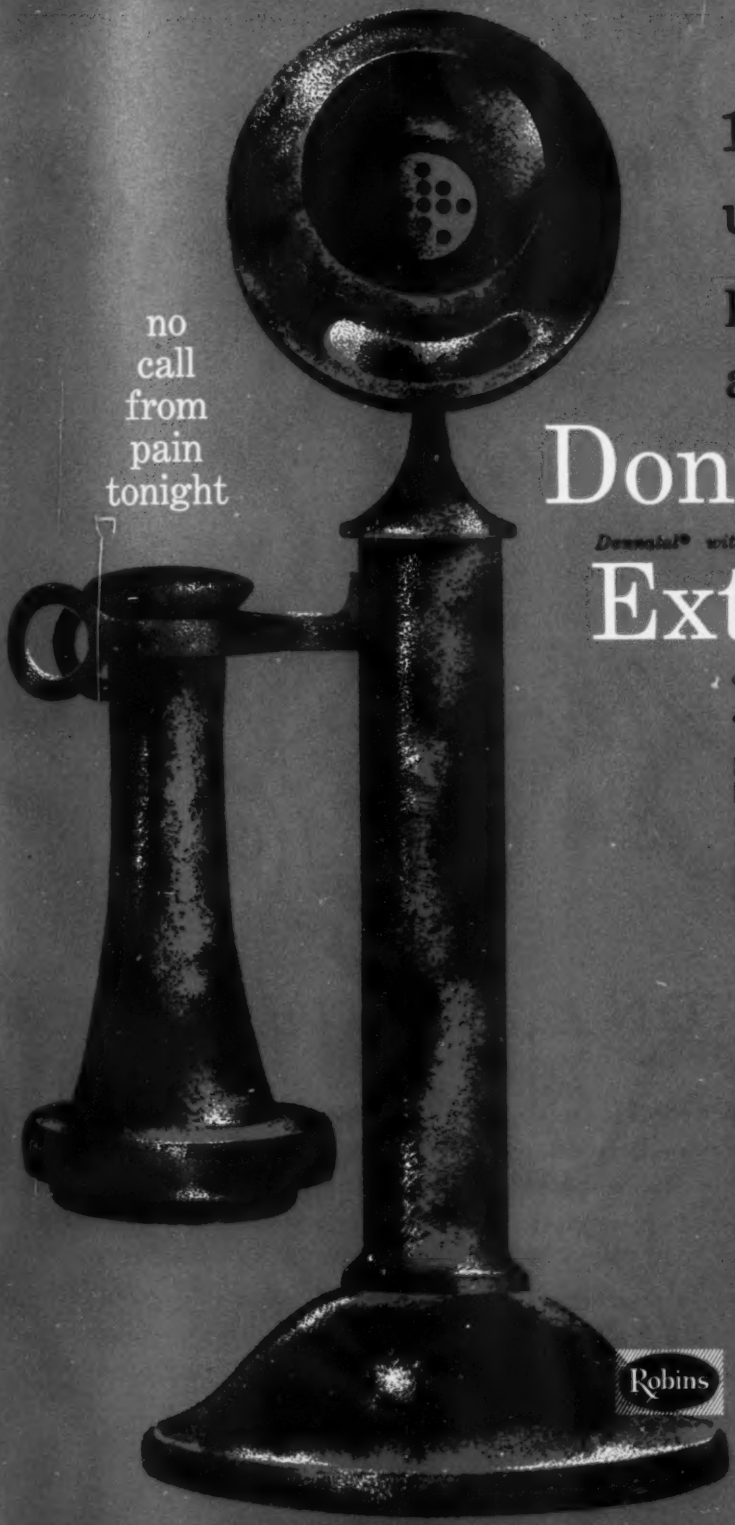
Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

*TRADEMARK


even,
mild
daytime
sedation
SOLFOTON
even, mild sedation
free from side effects
One tablet or capsule
T.I.D.
TABLETS
CAPSULES
Wm. P. Poythress & Co. Inc.
1856 100th Anniversary 1956

for the first time...extended action codeine



no call from pain tonight

10 to 12 hours uninterrupted pain relief in a single tablet

Donnagesic™

Donnatal® with Codeine extended action tablets

Extentabs*

- no up-and-down analgesia
- better codeine toleration

Belladonna alkaloids and phenobarbital, as in Donnatal, induce mild sedation, reducing pain consciousness and anxiety. Patient is protected from spasm. Codeine constipation, nausea and vomiting are avoided. Phenobarbital directly augments the potent analgesic effect of codeine.[1] Indicated wherever codeine is indicated—in pain or cough.

Donnagesic No. 1 (pink)

CODEINE Phosphate (¼ gr.)	48.6 mg.
Hyoscyamine Sulfate	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.)	48.6 mg.

Donnagesic No. 2 (red)

CODEINE Phosphate (1½ gr.)	97.2 mg.
Hyoscyamine Sulfate	0.3111 mg.
Atropine Sulfate	0.0582 mg.
Hyoscine Hydrobromide	0.0195 mg.
Phenobarbital (¼ gr.)	48.6 mg.

1. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, N. Y., The Macmillan Co., 1955, p. 187

Robins

A. H. ROBINS CO., INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit Since 1878

*TM Reg. U.S. Pat. Off. – pat. applied for

Combined for a ... on resistant ...

new

METRETON *tablets*

METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

For prompt and effective relief, especially in many resistant allergic disorders, METRETON affords the benefits of two established agents with unexcelled anti-inflammatory, anti-allergic and antipruritic effectiveness. ***supported by essential vitamin C*** —for stress support and for postulated effect on prolonging steroid action ***no better corticosteroid*** —original brand of prednisone...minimal electrolyte effects—METICORTEN ***no better antihistamine*** —unexcelled in potency and freedom from side effects—CHLOR-TRIMETON effective against hay fever, pollen asthma, perennial rhinitis, acute and chronic urticaria, angioneurotic edema, drug reactions, inflammatory and allergic eye disorders, pruritic and contact dermatoses.

formula: Each tablet of METRETON provides 2.5 mg. of METICORTEN (prednisone), 2 mg. of CHLOR-TRIMETON maleate (chlorprophenpyridamine maleate), and 75 mg. ascorbic acid.

supplied: METRETON Tablets, bottles of 30 and 100.

frontal attack

allergies

new

METRETON *nasal spray*

METICORTELONE (PREDNISOLONE) PLUS CHLOR-TRIMETON

quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

Packaging: 15 cc. plastic "squeeze" bottle, box of 1.

METRETON,* brand of corticoid-antihistamine compound; METICORTEN,* brand of prednisone; METICORTELONE,® brand of prednisolone; CHLOR-TRIMETON,® brand of chlorprophenpyridamine preparations. *T.M.

MT-J-876

Schering

a new clinical study[1]

adds to the growing promise of

Sparine*

HYDROCHLORIDE

Promazine Hydrochloride

10-(γ-dimethylamino-n-propyl)-phenothiazine hydrochloride

*Trademark

in a diversity

of common clinical conditions

1. Shea, J., et al., Military Med. 119:221-227 (Oct.) 1956.

Wyeth

Philadelphia

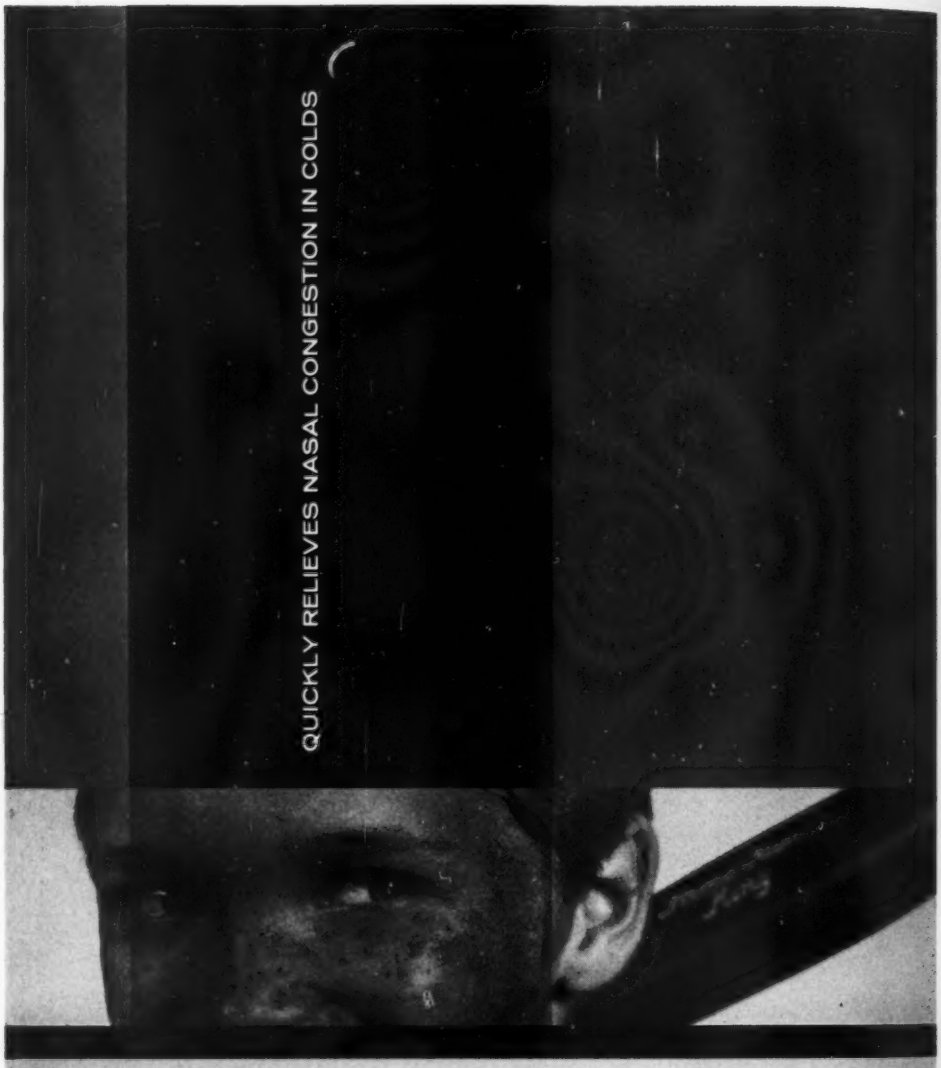
● SPARINE Hydrochloride provides dramatic control of agitation in the acute psychotic, acute alcoholic, and drug addict. Especially promising has been the minimal toxicity observed—no case of liver damage has been reported.

In a new study, Shea and others[1] find SPARINE effective for control of a wide range of conditions associated with various medical emergencies. In a series of 47 cases the authors found:

"On all but 2 cases the doses used (25 to 200 mg.) permitted satisfactory control of such . . . problems as agitation, anxiety, nausea, vomiting, pain and hiccoughs."[1]

Clinical Report on . . .

Case No.	Age	Diagnosis	Therapeutic Indication	Dose and Route	Duration of Therapy in Days	Response
1	56	Tetanus	Control convulsions and for relaxation	100 mg., q4h, I.V.	2	Good muscle relaxation Opisthotonos—no convulsions
2	36	Duodenal ulcer, D.T.'s	Control D.T.'s and nausea	50 mg., q6h, p.o.	6	No trouble with nausea
3	60	Peptic ulcer and hiatal hernia	For sedation	50 mg., q6h, p.o.	13	Good response—no pains
4	45	Pancreatitis—Gastritis	Hyperactivity	50 mg., q8h, p.o.	7	Good response—pain diminished
				50 mg., q4h, I.M.	7	
7	40	Intracranial hemorrhage and M.S.	Pain in muscles	50 mg., q.i.d., p.o.	35	Good control of muscle pain
8	30	Ulcerative colitis	Pain from muscle and vomiting	100 mg., q6h, I.M.	36	Fair response
9	38	Sickle cell crisis Narcotic addict	Control pain	100 mg., q4h, p.o.	3	Good response
10	48	Rt. lower lobe pneumonia Chronic alcoholic	Control activity	100 mg., q6h, p.o.	12	Good response
11	44	Pneumonia	Vomiting and D.T.'s	50 mg., q6h, I.M.	6	Good response, immediate
			Abdominal pain		10	Good pain control
22	13	Uremia	Vomiting	25 mg., q6h	4	Vomiting controlled
23	57	Alcoholic (post)	D.T.'s and pain in chest	50 mg., q.i.d., I.M.	25	Controlled D.T.'s, pain relieved
24	42	Alcoholic (post)	Confused and disoriented	50 mg., q6h, p.o.	27	Fair control
25	71	HCVD—cerebral arteriosclerosis	Behavior problem	50 mg., t.i.d., p.o.	9	Good
26	47	Rheumatoid arthritis Acute excitation	Pain	50 mg., q6h, p.o. 50 mg., q6h, p.o.	3 5	Fair response
27	16	Stricture of esophagus Pregnancy—hypertension	Vomiting	50 mg., q6h, I.M. 25 mg., q6h, I.M.	2 3	Controlled vomiting
		Chronic glomerulonephritis	Control nausea and vomiting	50 mg.	9	Good



Rhinall Nose Drops for Sinusitis, Allergic Rhinitis and Colds

Safe for children and adults
No burning or irritation
No bad taste or after reactions
No risk of sensitization

For convenience, also available in ½ ounce plastic spray bottle.

RHINOPTO COMPANY, DALLAS, TEXAS

Ethical Specialties for the Profession

5 way effectiveness with

trichotine*

in vulvovaginal therapy

1. *Trichotine is a detergent*
2. *Trichotine is a bactericide and fungicide*
3. *Trichotine is an aid to epithelization*
4. *Trichotine is an antipruritic*
5. *Trichotine is an aesthetic and psychosomatic adjunct*

Trichotine—more than a decade ago—pioneered in incorporating the multiple advantages of sodium lauryl sulfate with the recognized values of other specific or adjunctive agents for vulvovaginal therapy.

Trichotine douches may be prescribed as often as required—excellent for postcoital or postmenopausal hygiene—concentrated solutions useful for office clean-up or swab treatments. Acts quickly, safely, thoroughly.

Indications:

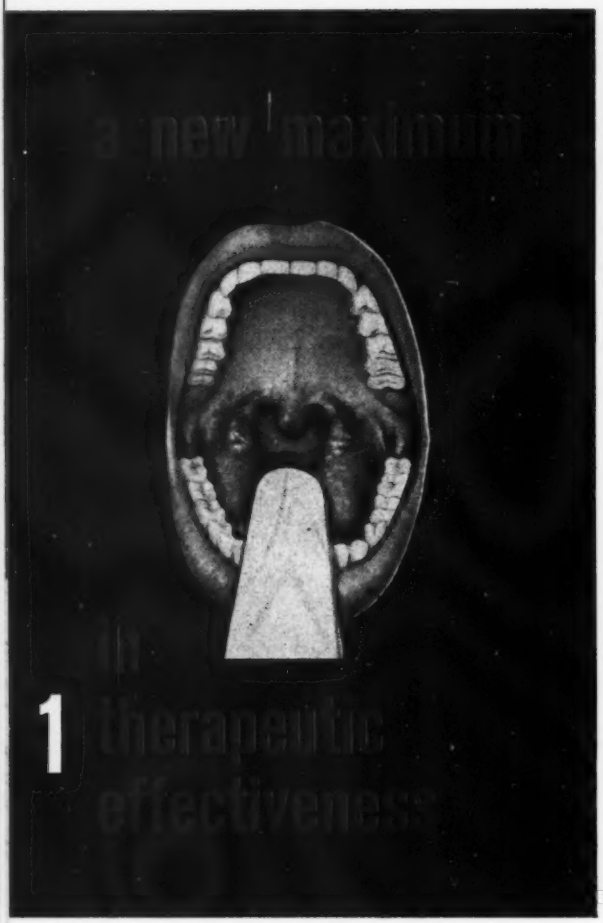
Non-specific vaginitis and leukorrhea, subacute and chronic cervicitis, senile vaginitis, pruritus vulvae, trichomoniasis, moniliasis.

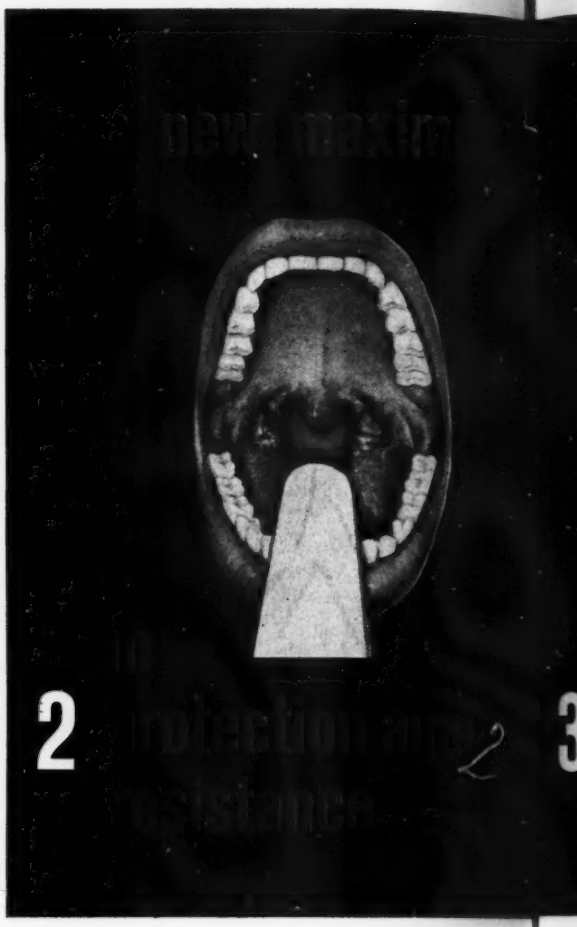
**Reg. U. S. Pat. Off.*

The Trichotine formula contains sodium lauryl sulfate, sodium perborate, sodium borate, thymol, eucalyptol, menthol, and methyl salicylate.

Samples and literature on request / Full details in P D R
Available in jars of 5, 12, and 20 oz.

the fesler co., inc. 375 Fairfield Ave., Stamford, Conn.





NEW Sigma

to meet threq

OLEANDOMYCIN TETRACYCLINE

World
Develo

in antibiotic therapy...
particularly for the 90% of
patients treated
at home or in the office...

as in the treatment of upper respiratory tract infections

The new synergistic formulation of tetracycline with oleandomycin (Matromycin®) brings to antibiotic therapy a new extended antimicrobial spectrum which includes even "resistant" staphylococci, while it provides protection against the emergence of *new* resistant strains. Indicated in infections of the upper respiratory tract and related structures, such as: sinusitis, tonsillitis, pharyngitis, bronchitis, otitis media, pleurisy.

Supplied: Capsules, 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.).

requirements of antibiotic therapy today

amycin*

synergistically strengthened multi-spectrum antibiotic formulation

World Leader in Antibiotic Development and Production

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

*TRADEMARK

all through the night

one application of

DESITIN®

OINTMENT

helps protect the infant's skin against

diaper rash (ammoniacal dermatitis) • **irritation** • **excoriation**

DESITIN OINTMENT covers the infant's skin with a soothing, protective, healing coating which is largely impervious to and helps guard against irritation, rash, and maceration caused by urine, excrement, perspiration and secretions. This preventive action of Desitin Ointment *persists all through the night*... when baby is particularly vulnerable to painful skin excoriations.

Nonsensitizing, nonirritant Desitin Ointment.. **rich in cod liver oil** .... successfully used on millions of infants for over 30 years.

- tubes of 1 oz., 2 oz., 4 oz.
- 1 lb. jars.

for **samples** *and literature please write....*

DESITIN CHEMICAL COMPANY 70 Ship Street Providence 2, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. **2.** Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. **3.** Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. **4.** Turell, R.: New York St. J. Med. 50:2282, 1950. **5.** Marks, M. M.: Missouri Med. 52:187, 1955.

new

When you prescribe Lipo Gantrisin, your patients usually need only two doses daily, for the antibacterial action of a single dose

LIPO GANTRISIN 'Roche'

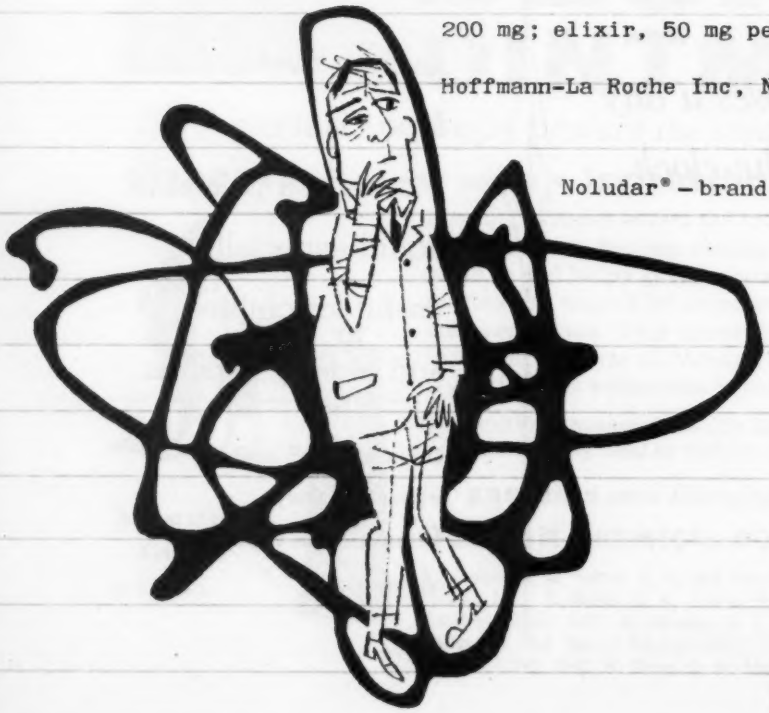
lasts for twelve hours. Lipo Gantrisin 'Roche' is a palatable liquid especially useful for children and elderly invalids.

Only two doses a day for round-the-clock effect

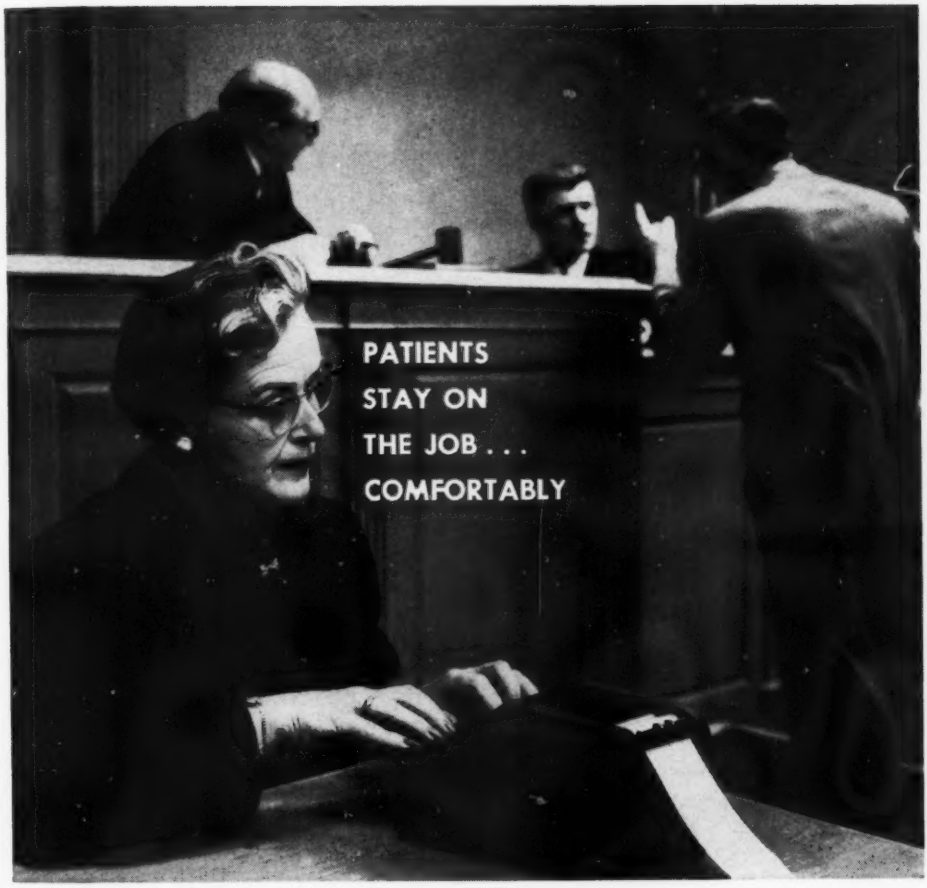
Lipo Gantrisin® Acetyl —brand of acetyl sulfisoxazole in vegetable oil emulsion

For patients wound up in a tangle of nerves—

Noludar 'Roche' provides relaxation. Not a barbiturate, not habit forming, 50 mg t.i.d. brings daytime sedation without undue drowsiness, while 200 mg h.s. usually induces a restful night's sleep with a clear-headed awakening. Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoonful. Hoffmann-La Roche Inc, Nutley, N.J.



Noludar®—brand of methyprylon



in URINARY DISTRESS

Pyridium®

(Brand of Phenylazo-diamino-pyridine HCl)

provides gratifying relief in a matter of minutes

Painful symptoms impel the patient with acute or chronic pyelonephritis, cystitis, urethritis or prostatitis to seek your aid. In the interval before antibiotics, sulfonamides or other antibacterial measures can become effective, the nontoxic, compatible, analgesic action of PYRIDIUM brings prompt relief from urgency, frequency, dysuria, nocturia or spasm. At the same time, PYRIDIUM imparts an orange-red color to the urine which reassures the patient. Used alone or in combination with antibacterial agents, PYRIDIUM may be readily adjusted to each patient by individualized dosage of the total therapy.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets in vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

MERCK SHARP & DOHME
Philadelphia 1, Pa.
Division of MERCK & CO., INC.

in those intranasal disorders

where thick mucopurulent discharge indicates there is secondary bacterial infection, prescribe

'*Trisocort*' *Spraypak is the intranasal preparation which provides:**

(*a*) ***Hydrocortisone***— **the most effective intranasal anti-inflammatory agent: to reduce inflammation, edema, and engorgement.**

(*b*) ***3 antibiotics***— **gramicidin, polymyxin and neomycin: to neutralize both gram-positive and gram-negative bacteria.**

(*c*) ***2 decongestants***— **phenylephrine hydrochloride and Paredrine† Hydrobromide: to assure both rapid and prolonged decongestion.**

Formula: Hydrocortisone alcohol, 0.02%; gramicidin, 0.005%; neomycin sulfate (equivalent to neomycin base, 0.60 mg./cc.); polymyxin, 2000 U/cc.; phenylephrine hydrochloride, 0.125%; 'Paredrine' Hydrobromide, 0.5%; preserved with thimerosal, 1:100,000. Available in ½ fl. oz. squeeze bottles.

Smith, Kline & French Laboratories, Philadelphia 1

*Trademark
†T.M. Reg. U.S. Pat. Off. for hydroxyamphetamine hydrobromide, S.K.F.

IN
GASTROINTESTINAL
SPASM

Barbidonna®

offers the logical combination of natural belladonna alkaloids and phenobarbital—a combination which provides smooth spasmolysis and balanced sedation.

EACH TABLET OR FLUIDRAM OF ELIXIR CONTAINS:

PHENOBARBITAL .....16 mg. (¼ gr.)

BELLADONNA ALKALOIDS .....0.13 mg.

(Incorporated as Hyoscyamine sulfate 0.1286 mg. Atropine sulfate 0.0250 mg. and Scopolamine hydrobromide 0.0074 mg.; approximately equivalent to 7 min. Tr. Belladonna.)

VANPELT & BROWN, INC. Richmond, Virginia

for controlled diuresis

Diamox*

Acetazolamide Lederle

Non-toxic
Non-mercurial
Simple, oral dosage

DIAMOX is an inhibitor of the enzyme carbonic anhydrase; it is not a mercurial or xanthine derivative. It causes prompt, ample diuresis, but its effect lasts only six to twelve hours. As a result, the patient taking DIAMOX in the morning is assured a normal, uninterrupted night's rest.

DIAMOX is not toxic, nor does it accumulate in the body, and patients are slow to develop a tolerance for it. This remarkable drug is therefore well-suited to long-term treatment. Dosage is simple and convenient: one tablet taken orally, each or every other morning.

Indications: cardiac edema, premenstrual tension, acute glaucoma, epilepsy, obesity, and the toxemia and edema of pregnancy.

NOW THE MOST WIDELY PRESCRIBED ORAL DIURETIC!

Tablets of 250 mg. (also in ampuls of 500 mg. for parenteral use when oral ingestion is impractical.)

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y. Lederle

*REG. U. S. PAT. OFF.

Establishing desired eating patterns

Obedrin®

and the 60-10-70 Basic Plan

In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

Obedrin contains:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

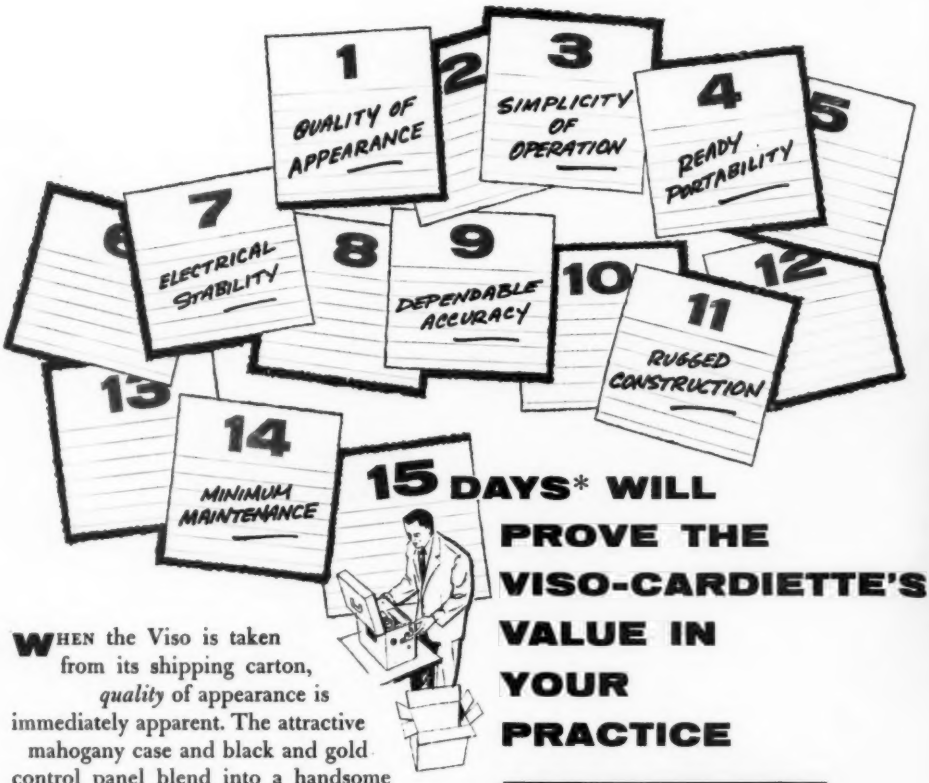
Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE



DAYS* WILL PROVE THE VISO-CARDIETTE'S VALUE IN YOUR PRACTICE

WHEN the Viso is taken from its shipping carton, *quality* of appearance is immediately apparent. The attractive mahogany case and black and gold control panel blend into a handsome appearance which, in itself, is actually an operating advantage, since it helps to reduce apprehensiveness in "new" ECG patients.

The first days of your use of the Viso clearly reveal its simple, quickly learned operation. And, as the days of the "trial period" go by, other features of this instrument become obvious: freedom from "AC" interference, complete stability of operation, "rugged" nature of Viso construction, easy portability of the instrument.

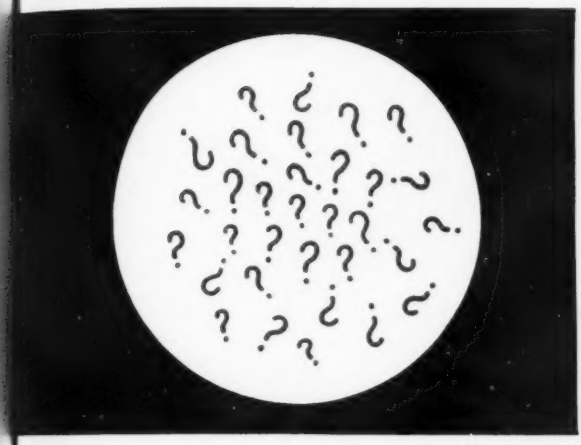
In reviewing the many advantages of Viso ownership, a thought about future service and supplies may occur to you. For Sanborn owners, service is typified in the informative, bi-monthly Technical Bulletin sent free of charge to all Sanborn owners . . . by capably staffed Branch Offices and Service Agencies in *42 cities* throughout the country . . . and by Sanborn's reputation as a manufacturer of precision medical diagnostic instruments since 1917.

*Sanborn Company offers you a Viso-Cardiette to use in your own practice for 15 days — without cost or obligation — to let your own experience decide IF an ECG would be useful to you, and if so, WHICH one.

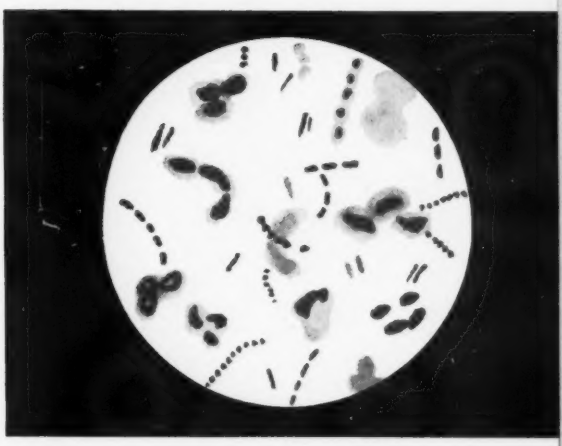
SANBORN COMPANY
WALTHAM 54, MASSACHUSETTS

COMBINED ACTION FOR DECISIVE CONTROL

IN UNDIAGNOSED INFECTIONS



IN MIXED BACTERIAL INFECTIONS



- Wide antibacterial spectrum for control over a wide range of gram-positive and gram-negative infections
- Effective blood levels for high therapeutic activity
- High urinary solubility, low renal risk
- Special alumina-gel base* for uniform dispersion and rapid absorption

Supplied: Tablets BICILLIN-SULFAS, bottles of 36. Suspension BICILLIN-SULFAS, bottles of 2 and 3 fl. oz. Each tablet and each 5-cc. teaspoonful contains 150,000 units of BICILLIN and 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine.

*In Suspension only

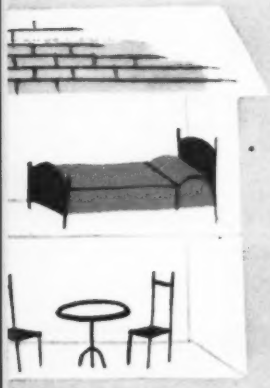
TABLETS SUSPENSION

BICILLIN® -SULFAS

Benzathine Penicillin G (Dibenzylethylenediamine Dipenicillin G) and Triple Sulfonamides

Wyeth

Philadelphia 1, Pa.



she's heard the call

for

VI-DAYLIN®

Each 5-cc. teaspoonful of VI-DAYLIN contains:

Vitamin A	3000 U.S.P. units (0.9 mg.)
Vitamin D	800 U.S.P. units (20 mcg.)
Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Pyridoxine Hydrochloride	1.0 mg.
Ascorbic Acid	40 mg.
Vitamin B_{12}	3 mcg.
Nicotinamide	10 mg.

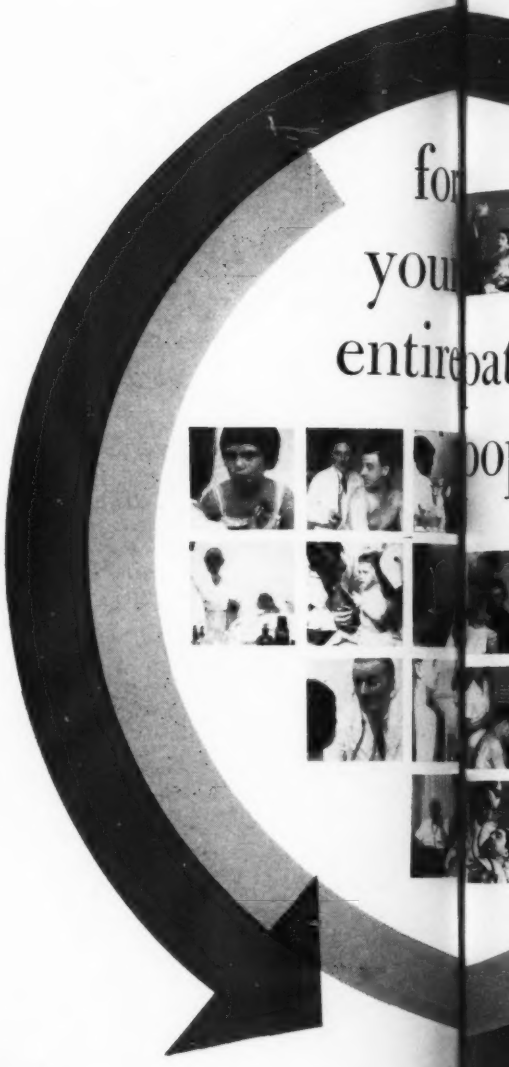
Abbott

a new maximum
in therapeutic
effectiveness

a new maximum
in protection
against
resistance

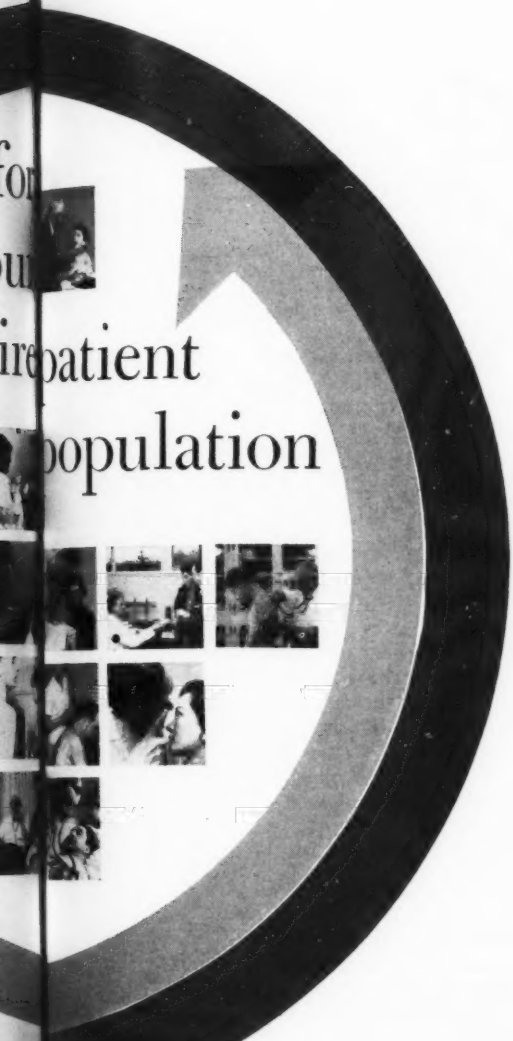
a new maximum
in safety and
toleration

multi-spectrum
synergistically
strengthened...



Sigma

OLEANDOMYCIN TETRACYCLINE



a new certainty

in antibiotic therapy, particularly for the 90% of patients treated at home and in the office

Superior control of infectious diseases through superior control of the changing microbial population is now available in a new formulation of tetracycline, outstanding broad-spectrum antibiotic, with oleandomycin, Pfizer-discovered new antimicrobial agent which controls resistant strains. The synergistic combination now brings to antibiotic therapy: (1) a new fuller antimicrobial spectrum which includes even "resistant" staphylococci; (2) new superior protection against emergence of *new* resistant strains; (3) new superior safety and toleration.

mycin*

*TRADEMARK

Pfizer

HOW OLD IS OLD?

"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adolescence and senescence."[3]

"One finds alert, interesting, active folks in the 80's and, on the other hand, there are people in the 20's and 30's who have all the characteristics of old age."[4]

THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth – perhaps most important – is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

NEOBON'S COMPREHENSIVE FORMULA

NEOBON®, a product of Roerig research, is a blended combination of the five most commonly indicated factors for prevention or treatment of the nonacute conditions of aging. Each soft, soluble capsule provides:

Non-stimulatory gonadal hormone replacement

balanced hematinic component

digestant enzyme replacement

specially formulated mineral-vitamin combination

new lysine, for protein improvement*

* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics." Such people have much to gain from NEOBON therapy. The rewards are fuller, more active, more pleasurable years for patients past 40. The daily dose (3 capsules) of NEOBON provides:

L-lysine	150 mg.
Methyltestosterone	3 mg.
Ethinyl Estradiol	0.018 mg.
Pancreatic Substance***	150 mg.
Glutamic Acid	90 mg.
Rutin	15 mg.
Vitamin A (Palmitate)	6,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	600 U.S.P. Units
Vitamin E (as Tocopheryl Acetate)	15 I.U.
Calcium Pantothenate	15 mg.
Thiamine Mononitrate (Vitamin B_1)	1.5 mg.
Riboflavin (Vitamin B_2)	1.5 mg.
Pyridoxine Hydrochloride (Vitamin B_6)	1.5 mg.
Niacinamide	150 mg.
Ascorbic Acid (Vitamin C)	150 mg.
Vitamin B_{12} (Oral Concentrate)	3 mcg.
Folic Acid	0.3 mg.
Liver-Stomach Substance**	300 mg.
Iron (from Ferrous Gluconate)	10.2 mg.
Cobalt (from Cobaltous Sulfate)	0.1 mg.
Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
Iodine (from Potassium Iodide)	0.15 mg.
Potassium (from Potassium Sulfate)	5 mg.
Zinc (from Zinc Sulfate)	1.2 mg.

**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.

***Enzymatically active defatted material obtained from 750 mg. of whole fresh pancreas.

Dosage: 3 capsules daily, with meals.

Supplied: Bottles of 60 capsules, prescription only.

NEW NEOBON® LIQUID

A GERIATRIC TONIC

Now also available for your consideration is NEOBON LIQUID, which provides hematinic action, improved carbohydrate and protein utilization, gonadal and thyroid hormone supplementation and a mild antidepressant action.

The pleasant tasting liquid is especially indicated when a combined attack against nutritional, physiological and mental depression is indicated. Each teaspoonful (5 cc.) of pleasant-tasting NEOBON LIQUID contains:

Ferrous Gluconate	30 mg.
Ascorbic Acid	50 mg.
d-Amphetamine Sulfate	0.5 mg.
Folic Acid	167 mcg.
Vitamin B_{12}	2.5 mcg.
l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

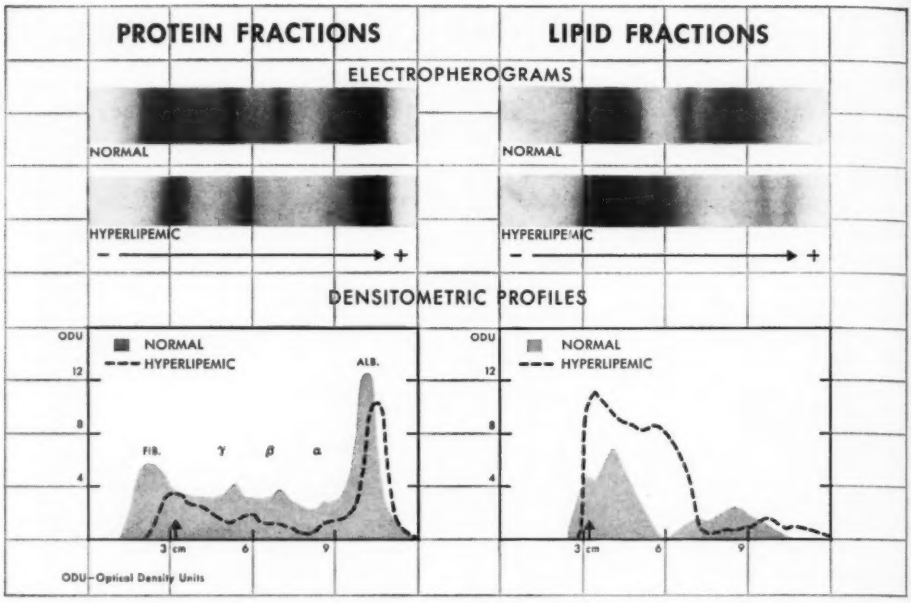
Dosage: One teaspoonful twice daily before meals, or as required.

Supplied: In 16 fluid ounce bottles, prescription only.

Bibliography

1. Anonymous. 2. Rosenthal, P.: Geriatrics 10:382 (August) 1955. 3. Lansing, A. I.: Symposium on Problems of Gerontology, National Symposium Series No. 9 (August) 1954. 4. Mason-Hohl, E.: Quoted in W. Va. Med. J. 51:16 (January) 1955. 5. Rosenberg, H. R., et al.: Arch. Biochem. and Biophys. 49:263, 1954. 6. Bricker, M., Mitchell, H. H. and Kinsman, G. M.: J. Nutrition 30:269, 1945. 7. Masters, W. H. and Ballew, J. W.: Geriatrics 10:1, 1 (January) 1955.

ROERIG *CHICAGO 11, ILLINOIS*



BLOOD DRAWS ITS OWN PROFILE

Here's one of the most ingenious methods of blood analysis! A small strip of paper in an electric field paints a picture that's worth a thousand calculations!

Principle: **The phosphatides and phosphatide-containing complexes travel along the electrified path of the paper strip allowing identifiable protein and lipid complexes to be deposited at various points. Where the phosphatide content is insufficient, electroneutral lipids (cholesterol, neutral fat) are set free to remain at the starting point. Thus we obtain the characteristic tell-tale density zones of the electrophoretic profile.**

Significance: **Paper electrophoresis provides demonstrable physical evidence in disturbances of lipid metabolism and in associated disease states. Characteristic patterns have been obtained in hypercholesteremia, hyperlipemia, lipoid nephrosis, etc.; electrophoretic profiles from various species illustrate their relative predisposition to atherosclerosis.**

Application: **Paper electrophoresis is now being used to investigate the influence of dietary supplementation with "RG" Lecithin upon lipoprotein patterns in patients with lipid metabolism disturbances.**

Glidden's "RG" Lecithin **consists of 90% natural phosphatides in dry, free-flowing granules refined from soybeans. It is the only lecithin made expressly for medically indicated dietary purposes.**

"RG" Lecithin **is well tolerated and readily utilized by the body. *There are no contraindications.* Daily dietary supplement: 1 tablespoonful (7.5 Gm.) in juices or on cereals. (Up to 60 Gm. daily are used in clinical trials.)**

Literature on lecithin in health and disease available on request.

RG® LECITHIN **A dietary phosphatide supplement.**

The Glidden Company · **Chemurgy Div., 1825 N. Laramie Ave., Chicago 39, Ill.**

For patients with Advanced Hypertension who require

Combination Therapy

RAUWILOID® (alseroxylon) is recognized as basal medication in all grades and types of hypertension. Alone, it controls most mild, labile cases. When more potent agents are required, their combination with Rauwiloid permits smaller doses with resultant reduction or elimination of side effects, and a more stable, dependable therapeutic response.

RAUWILOID + VERILOID® in single-tablet form is indicated in moderate to severe hypertension. The combination permits long-term therapy with lower doses of Veriloid (alkavervir), greatly lessened side effects, and dependably stable response. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid. Initial dose, 1 tablet t.i.d., p.c.

RAUWILOID + HEXAMETHONIUM in single-tablet combination provides smoother, less erratic response to oral hexamethonium. Indicated in severe, otherwise intractable hypertension. The combination permits up to 50% less hexamethonium to exert full effect. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, 1/2 tablet q.i.d.

Riker

LOS ANGELES

now you can prescribe

4 sulfas

in a delicious suspension... no unpleasant aftertaste

DELTAMIDE®

THE PREFERRED QUADRI-SULFA MIXTURE

Suspension Tablets

Finicky patients are on your side when you prescribe Deltamide Suspension. Its delightful synthetic chocolate-like flavor completely masks the taste of sulfas. Deltamide Suspension can safely be given to children and other patients sensitive to chocolate.

Try Deltamide in urinary tract infections. Action is rapid and side effects rare. Deltamide is economical for your patients.

Each 5 cc. teaspoonful of the Suspension, or each Tablet, supplies:

Sulfadiazine	0.167 Gm.
Sulfamerazine	0.167 Gm.
Sulfamethazine	0.056 Gm.
Sulfacetamide	0.111 Gm.

Tablets: Bottles of 100 and 1000.
Suspension: 4 and 16 oz. bottles.

When the situation also calls for penicillin—
DELTAMIDE w/Penicillin

Each tablet or 5 cc. of suspension contains—in addition—250,000 units of potassium penicillin G.

Tablets: Bottles of 36 and 100. Powder for suspension: 60 cc. bottles to provide 2 oz. of suspension by adding 40 cc. of water.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY. • KANKAKEE, ILLINOIS

effective[1] in over

91% of cases

Terra-Cortril®

brand of oxytetracycline and hydrocortisone

Topical Ointment

Proved effective in 526 of 575 cases of varied dermatoses. "No adverse reactions were noted..." in the entire group.[1]

"This topical ointment is clearly advantageous in combining in one preparation hydrocortisone [CORTRIL®]...and oxytetracycline [TERRAMYCIN®], which is effective against many of the pathogens that commonly exist with pruritic dermatoses."[2]

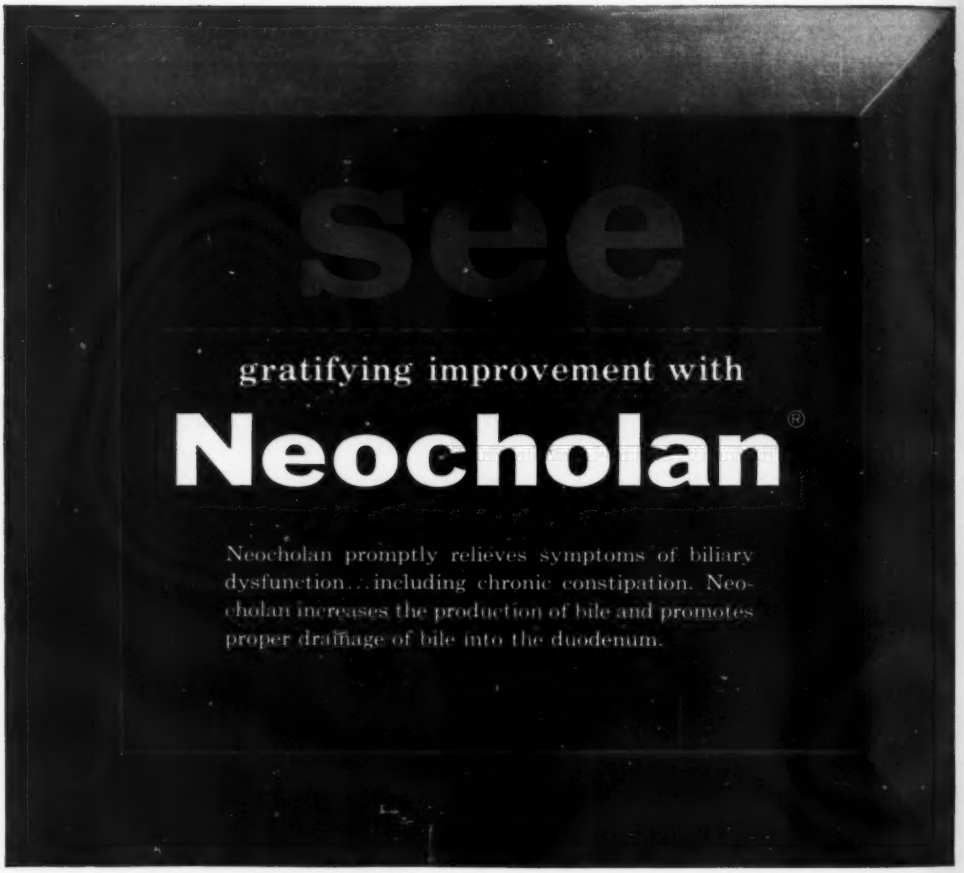
Supplied: In 1/2-oz. tubes, containing 3% oxytetracycline hydrochloride (TERRAMYCIN) and 1% hydrocortisone (CORTRIL).

Pfizer **PFIZER LABORATORIES,** *Brooklyn 6, New York*
Division, Chas. Pfizer & Co., Inc.

1. Robinson, R. C. V., and Robinson, H. M., Jr.: South. M. J. 49:260, 1956.
2. Lubowe, I. I.: To be published.

LOOK for other signs of biliary dysfunction in "chronic constipation" patients

Other symptoms of dyspepsia, such as flatulence, intestinal atony, and belching—along with the patient's chronic constipation—may indicate a functional disorder of the biliary tree.


see
gratifying improvement with
Neocholan®
Neocholan promptly relieves symptoms of biliary dysfunction . . including chronic constipation. Neocholan increases the production of bile and promotes proper drainage of bile into the duodenum.

1 or 2 Neocholan tablets t.i.d.—with meals—is the usual effective dosage. As symptoms improve the dose may be decreased to 1 or 2 tablets daily. Each Neocholan tablet supplies Dehydrocholic Acid 250 mg. (3¾ grs.); Homatropine Methylbromide 1.2 mg. (1/50 gr.); Phenobarbital 8.0 mg. (⅛ gr.). Bottles of 100 and 1000 coated, yellow tablets.

PITMAN-MOORE COMPANY *Division of Allied Laboratories, Inc.* **Indianapolis 6, Indiana**

Medihaler

Means self-powered, uniform, measured-dose inhalation therapy...

Medihaler

Means true nebulization. Each measured dose provides 5 to 8 times as many particles in the ideal size range as conventional nebulizers...

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate...

Medihaler

Means effective medications in an inert aerosol vehicle, in leakproof, spillproof, plastic-coated bottles...

Medihaler

Means utmost patient convenience—medication and Adapter together in plastic case, convenient for pocket or purse...

Medihaler

Means greater economy—no costly glass nebulizers to replace, and one inhalation usually suffices for prompt relief.

Medihaler

THE UNIQUE MEASURED-DOSE INHALATION METHOD

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

℞ Medihaler-Epi™

Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

℞ Medihaler-Iso™

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

℞ Medihaler Oral Adapter

Note: First prescription for Medihaler medications should include the desired medication and Medihaler Oral Adapter.

Oral Adapter made of hard plastic with no movable parts...foolproof...unbreakable and easily cared for by rapid rinsing...entire set, including medication, fits into neat plastic case small enough to be carried inconspicuously in pocket or purse...the smallest package for nebulization ever produced.

In Angina Pectoris

NEW Medihaler-Nitro™

Medihaler-Nitro is 1% octyl nitrite in nebulization form. Outstanding for the emergency relief of acute anginal pain. Each inhalation delivers precisely 0.25 mg. of octyl nitrite. By using the lungs as the most direct portal of entry, faster relief than from orally administered drugs is assured because of proximity of pulmonary and coronary circulations. Faster-acting than nitroglycerin. Fewer side effects than from nitroglycerin or amyl nitrite.

Only one or two inhalations necessary. One full minute should elapse between inhalations. In 10 cc. Medihaler bottle with metered-dose valve.

Riker

LOS ANGELES

relaxes
both mind
and
muscle

for the average patient in everyday practice

- well suited for prolonged therapy
- well tolerated, nonaddictive, essentially nontoxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: **anxiety and tension states, muscle spasm.**

THE ORIGINAL MEPROBAMATE

Miltown®

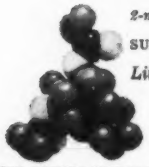
Tranquilizer with muscle-relaxant action

DISCOVERED AND INTRODUCED
BY WALLACE LABORATORIES, *New Brunswick, N. J.*

2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: *400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.*

Literature and Samples Available on Request



THE MILTOWN MOLECULE

CM-3706-R2

HARD-TO-KILL TRICHOMONADS

EXPLODE

WITHIN 15 SECONDS' CONTACT WITH VAGISEC LIQUID

WITH THE Davis technique,† using VAGISEC® liquid and jelly, flare-ups of vaginal trichomoniasis rarely occur. VAGISEC liquid actually explodes trichomonads within 15 seconds after douche contact.[1] Better than 90 per cent apparent cures follow use of this new trichomonacide,[2] developed as "Carlendacide" by Dr. Carl Henry Davis, noted gynecologist and author, and C. G. Grand, research physiologist.[3]

No trichomonad escapes—The overwhelming action of VAGISEC liquid dooms the trichomonad. One chelating agent and two surface-acting agents combine in attack to weaken the cell membrane, to remove waxes and lipid materials from the membrane surface, and to denature the protein. With its cell wall destroyed, the parasite imbibes water, swells and explodes. All this occurs within 15 seconds. Only scattered fragments remain.

No other agent or combination of agents kills the trichomonad in this specific fashion or with the *speed* of VAGISEC liquid.[3] When the patient uses VAGISEC jelly as well—the recommended routine—these good effects continue indefinitely.[4]

Reaches hidden trichomonads—Unlike many agents, VAGISEC liquid thoroughly penetrates and dissolves the cellular debris and mucoid material lining the vaginal surface.[3] It reaches hidden trichomonads—often the cause of treatment failure—as well as parasites swimming freely in the canal.

The Davis technique—Office therapy with VAGISEC liquid is combined with home treatment. Both liquid and jelly are prescribed.

OFFICE TREATMENT—*Wipe vaginal walls dry with cotton balls, then wash thoroughly for about three minutes with a 1:100 dilution of* VAGISEC *liquid. Remove excess fluid with cotton balls. Dr. Davis recommends three treatments the first week, two the second and one the third.*

HOME TREATMENT—*Patient douches with* VAGISEC *liquid every night or morning and then inserts* VAGISEC *jelly. Home treatment is continued through two menstrual periods, but omitted on office treatment days. Douching is contraindicated in pregnancy.*

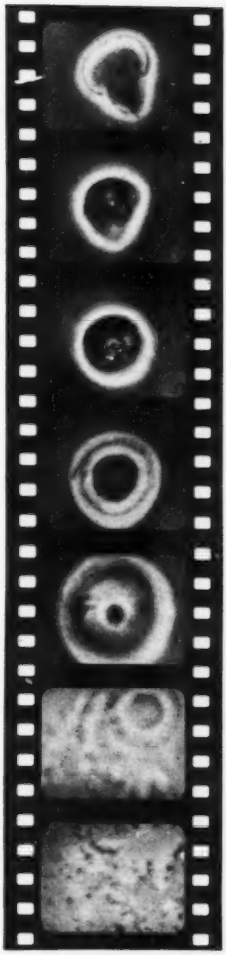
Husband re-infects wife—Since "trichomonads may be passed from the infected male to the uninfected partner during coitus,"[5] prevent re-infection by recommending the use of prophylactics. Specify RAMSES,® the finest possible rubber prophylactic, transparent, very thin yet strong; or XXXX (FOUREX)® skins, of natural animal membrane — pre-moistened. Your prescription of one of these brands insures the protection afforded by Schmid quality prophylactics and assures full acceptance of your regimen. At all pharmacies.

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Boric acid, Alcohol 5% by weight.

VAGISEC, RAMSES and XXXX (FOUREX) are registered trade-marks of Julius Schmid, Inc.

†Pat. App. for

JULIUS SCHMID, INC.
gynecological division
423 West 55th St., New York 19, N. Y.



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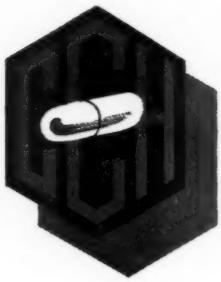
2 sec. CONTACTS
4 sec. COMPLEXES
6 sec. DISSOLVES
8 sec. DENATURES
10 sec. SWELLS
15 sec. EXPLODES
16 sec. SCATTERS

References: 1. Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955. 2. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955. 3. Davis, C. H., and Grand, C. G.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954. 4. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, Md., W. F. Prior, 1955, vol. 3, chap. 7, pp. 23-33. 5. Draper, J. W.: Internat. Rec. Med. *168*:563 (Sept.) 1955.



FOR NEARLY 20 YEARS

HASKELL'S

BELBARB

has provided Safe, Effective Spasmolysis and Sedation

NOW IN 5 CONVENIENT DOSAGE FORMS

	Phenobarbital	Belladonna Alkaloids	Supplied
1 BELBARB No. 1 per tablet	¼ gr.	hyoscyamine, atropine, and scopolamine in fixed proportion, approximately equivalent to Tr. Belladonna, 8 min.	Bottles of 100, 500 and 1,000 tablets
2 BELBARB No. 2 per tablet	½ gr.		Bottles of 100, 500 and 1,000 tablets
3 BELBARB-B with B Complex Supplement*	¼ gr.		Bottles of 100, 500 and 1,000 tablets
4 BELBARB Elixir per fluidrachm (4 cc)	¼ gr.		Bottles containing 1 pt. and 1 gal.
5 BELBARB Trisules	1 Trisule is equivalent to 3 Belbarb tablets		Bottles of 30 and 100 Trisules

*Thiamine Hydrochloride — 5 mg., Riboflavin — 2 mg., Calcium Pantothenate — 2.5 mg., Pyridoxine Hydrochloride — 0.5 mg., Niacinamide — 10 mg., Vitamin B_{12} Activity — 2 mcg.

Send for free samples and literature.

CHARLES C. HASKELL & CO., INC., Richmond, Virginia

Raise Pain Threshold...

Reduce Nervous Tension

RELIEVE TENSION HEADACHE

FIORINAL®

TABLETS

Dose: 1 or 2 tablets every four hours, as needed

Each tablet contains:

Sandoptal (Allylbarbituric acid *N.F. X)*	50 mg. (¾ gr.)
Caffeine	40 mg. (⅔ gr.)
Acetylsalicylic acid	200 mg. (3 gr.)
Acetophenetidin	130 mg. (2 gr.)

SANDOZ

Sandoz
PHARMACEUTICALS
HANOVER, N. J.

"Neither rain, nor snow, nor advancing years shall stay this courier!"

For persons past forty, good health is usually a source of great pride and satisfaction. Each succeeding year seems to heighten their delight and appreciation. To help these "senior citizens" maintain their vigor, prescribe GEVRAL, a comprehensive geriatric diet supplement that provides 14 vitamins, 11 minerals, and Purified Intrinsic Factor Concentrate—all in one convenient, *dry-filled* capsule.

Gevral*

GERIATRIC VITAMIN-MINERAL SUPPLEMENT LEDERLE

dry filled sealed capsules

for more rapid and complete absorption, freedom from after-taste. A Lederle exclusive!

Lederle LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, NEW YORK

*REG. U. S. PAT. OFF.

Each GEVRAL Capsule contains:

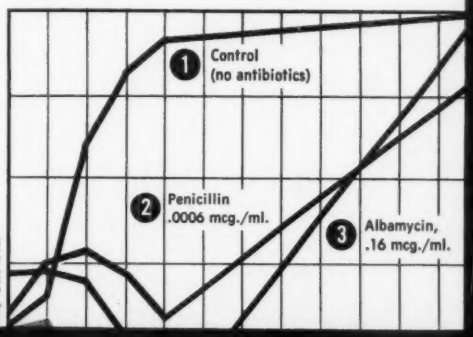
Vitamin A	5000 U.S.P. Units	Choline Dihydrogen Citrate	100 mg.	Calcium (as $CaHPO_4$)	145 mg.
Vitamin D	500 U.S.P. Units	Inositol	50 mg.	Phosphorus (as $CaHPO_4$)	110 mg.
Vitamin B_{12}	1 mcgm.	Ascorbic Acid (C)	50 mg.	Boron (as $Na_2B_4O_7.10H_2O$)	0.1 mg.
Thiamine Mononitrate (B_1)	5 mg.	Vitamin E (as tocopheryl acetates)	10 I.U.	Copper (as CuO)	1 mg.
Riboflavin (B_2)	5 mg.	Rutin	25 mg.	Fluorine (as CaF_2)	0.1 mg.
Niacinamide	15 mg.	Purified Intrinsic Factor Concentrate	0.5 mg.	Manganese (as MnO_2)	1 mg.
Folic Acid	1 mg.	Iron (as $FeSO_4$)	10 mg.	Magnesium (as MgO)	1 mg.
Pyridoxine HCl (B_6)	0.5 mg.	Iodine (as KI)	0.5 mg.	Potassium (as K_2SO_4)	5 mg.
Ca Pantothenate	5 mg.			Zinc (as ZnO)	0.5 mg.

Other Lederle geriatric products include: *GEVRABON Vitamin-Mineral Supplement Liquid with a wine flavor; *GEVRAL** Protein Vitamin-Mineral-Protein Supplement Powder; and *GEVRINE** Vitamin-Mineral-Hormone Capsules.**

Antibiotic Synergism

This graph shows the growth rate of a penicillin- sens
tive strain of Staphylococcus (Micrococcus pyogene
var. aureus) under 3 conditions:

1. In the absence of antibiotics
2. In the presence of subinhibitory concentration
   penicillin
3. In the presence of subinhibitory concentration
   Albamycin*



Now lift this transparency and see what happens when **half** these amounts of penicillin and Albamycin are **combined!**

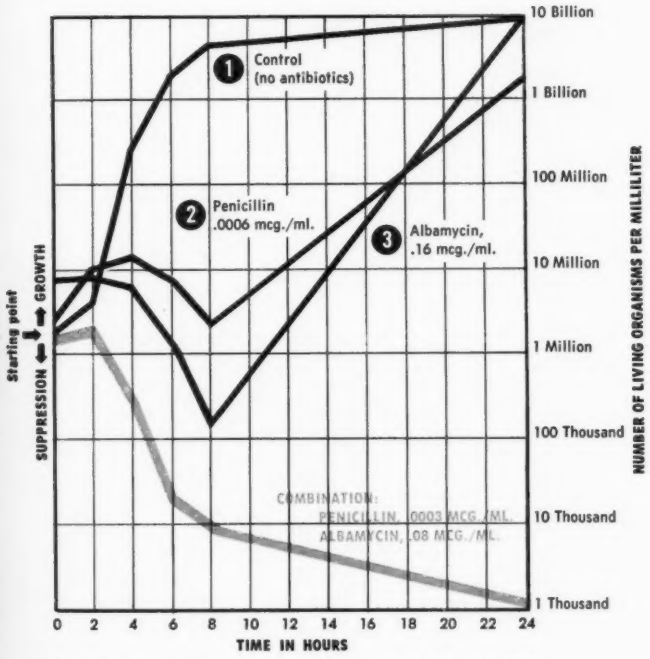
Upjohn

*Trademark, Reg. U.S. Pat. Off.—The Upjohn brand of crystalline novobiocin
Data: Upjohn Research Laboratories (3265—ARB—119)

Antibiotic Synergism

This graph shows the growth rate of a penicillin- sensitive strain of Staphylococcus (Micrococcus pyogenes, var. aureus) under 3 conditions:

1. In the absence of antibiotics
2. In the presence of subinhibitory concentration of penicillin
3. In the presence of subinhibitory concentration of Albamycin*



Even half these subinhibitory concentrations of penicillin and Albamycin, when combined, produce a dramatic bactericidal effect.

Such a product is available now

Upjohn

*Trademark, Reg. U.S. Pat. Off.—The Upjohn brand of crystalline novobiocin sodium.
Data: Upjohn Research Laboratories (3265—ARB—119)

average dosage only t.i.d.

New

Alba-Penicillin*

(Albamycin plus penicillin)

Compare it with the antibiotic you are currently using:

Range of effectiveness: Alba-Penicillin is effective against the organisms that cause the overwhelming majority of bacterial infections (Staphylococci, Streptococci, Pneumococci, Proteus).

Risk of resistance: Because in vitro tests show this combination is synergistic against even Staphylococci **already** resistant to all other antibiotics, the risk of resistance is minimized.

Risk of enterocolitis: Because it has little or no effect on the predominant Gram-negative intestinal bacteria, and is highly effective against Staphylococci, there is virtually no danger of enterocolitis due to alteration in intestinal flora, or of other side effects such as perianal pruritus.

Convenience: Alba-Penicillin is oral therapy, and the average adult dosage is only **1 to 2 capsules t.i.d.**, which eliminates middle-of-the-night medication.

It is available in bottles of 16 capsules. Each capsule contains 250 mg. Albamycin (as novobiocin sodium, crystalline) and 250,000 units penicillin G potassium.

Upjohn

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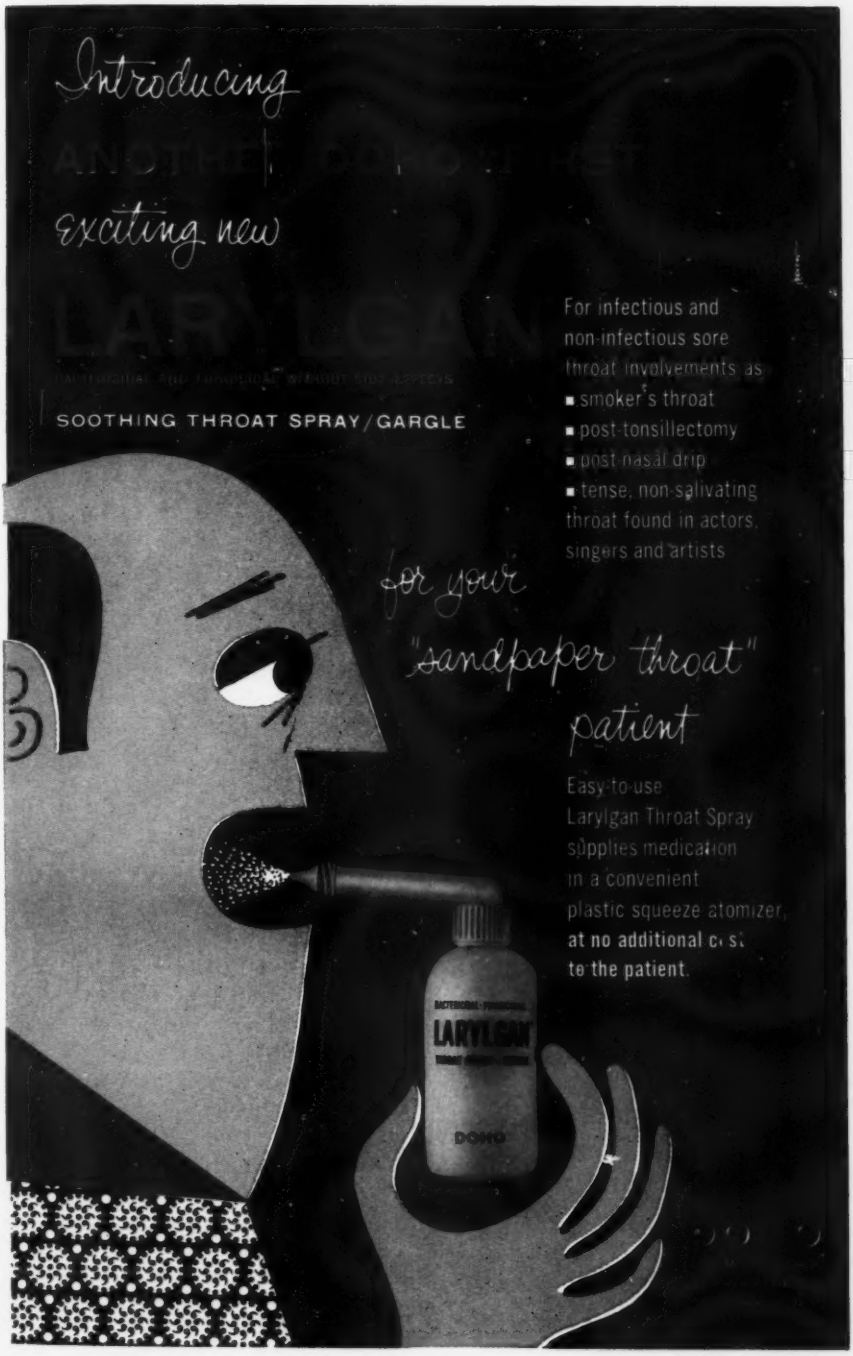
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1. Science News Letter, March 1954
2. Greenblatt, R. B.: Obstet. & Gyn. 2:530, 1953

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References: 1. Greenblatt, R.B.: Obst. & Gynec. *2*:530, 1953. 2. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 3. Barishaw, S. B.: Exp. Med. Surg. *7*:358, 1949. 4. Selsman, G. J. V. & Horoschak, S.: Am. J. Dig. Dis. *17*:92, 1950.

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Pediatric Bibliography

1. Wikler: The Use of Chlorpromazine as an Anti-emetic in Children, Arch. Pediat. 72:197 (June) 1955.
2. Daeschner et al.: Chlorpromazine in the Control of Vomiting in Children, Am. J. Dis. Child. 89:525 (May) 1955.
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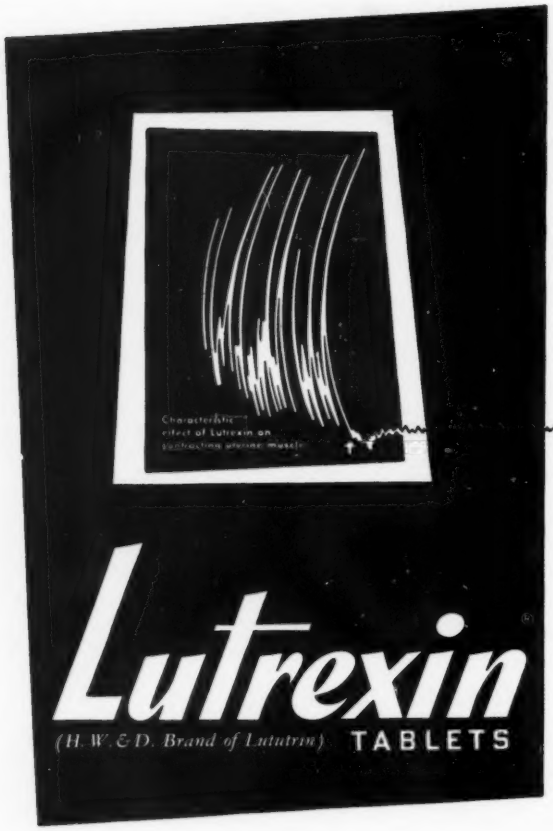

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1. *Jones, Georgeanna S. and Smith, Frank: Am. J. Obstet. Gynecol., Vol. 67: No. 3, 628-633, 1954.*
2. *Majewski, J. T. and Jennings, T.: Obstetrics & Gynecology, Vol. 5, No. 5, 1955.*

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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

December 1956

SYMPOSIUM ON THYROID

The clinical manifestations of diseases of the thyroid gland and their management, whether medical or surgical, are well recognized and generally well applied. However, the whole of thyroid function and the physiologic role of its hormone have never been completely clarified. Newer technics, using both radioactive isotopes and biochemistry, have provided tools for the study of the unknown in thyroidal function. This symposium provides for a presentation and discussion of much that is new in this field.

Physiology of the Thyroid Gland and its Hormone*

S. B. BARKER, Ph. D.,† *Birmingham, Ala.*

MANY OF THE CONTRIBUTIONS OF BASIC RESEARCH on the understanding of thyroid function which have resulted in better clinical procedures in both diagnosis and treatment are being discussed at these meetings. The time allotted to this presentation is much too limited to permit an adequate review of both the background and applied material, so the former will be stressed and the latter merely indicated. It will become apparent as we progress that there are many areas where further information is needed.

In order to present a well-rounded survey of thyroid function, the discussion will be divided (Fig. 1) into three parts: I. Production of the hormone by the thyroid gland; II. Circulation of the hormone in the blood stream; and III. Action of the hormone in peripheral tissues.

I. Function of the Thyroid Gland

So much stress has been placed on the specific role of the thyroid gland in the synthesis of thyroxine that it is not always realized that the gland has a highly specific iodide-trapping action.[1] Since this trapping involves iodine compounds from inorganic through a series of organic stages to thyroxine, it may well be that formation of the latter is actually a mass-action effect, less specifically related to the synthesis of thyroxine itself than to the overall retention of iodine. Of course, from the strictly practical point of view, the importance of synthesis of hormone by the thyroid gland takes precedence.

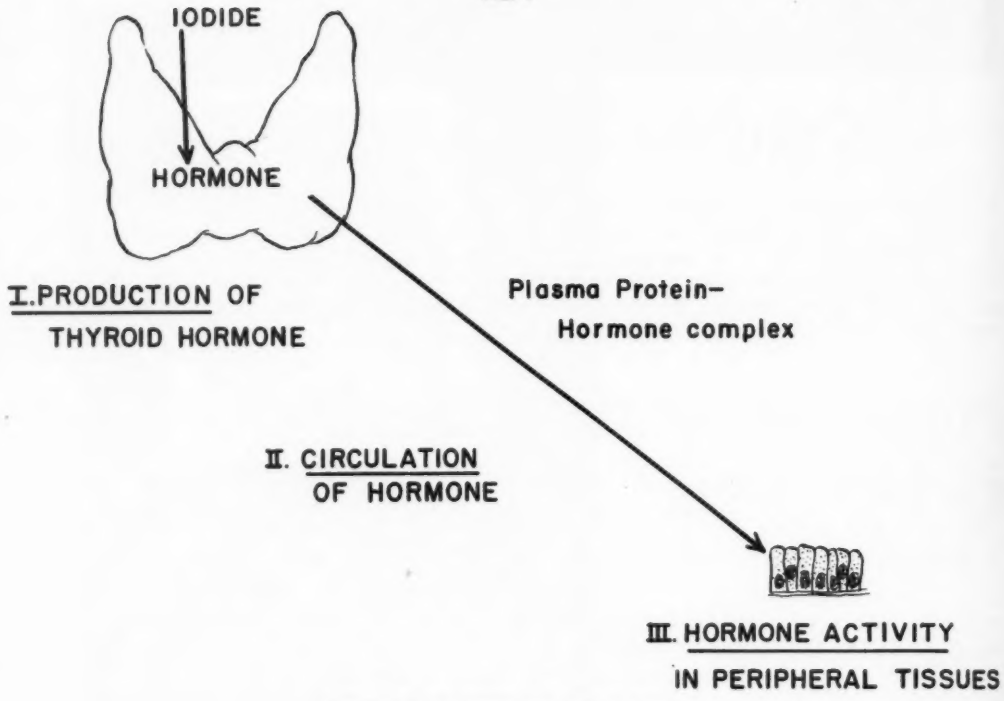
It has proved very difficult to obtain adequate detailed information concerning the enzymatic steps involved in fixing iodide. As indicated in figure 2, the rapid picking up ("trapping") of circulating iodide by the gland could be due to the activity of some type of specific transport mechanism in the cell membrane. This results in the accumulation of a loosely bound intracellular iodide. The transport mechanism can be swamped by iodide if the plasma level is elevated and is more specifically interfered with by perchlorate, thiocyanate and nitrate, in that order of effectiveness. The last three appear not to be concentrated by the thyroid, while iodide concentration to the extent of 25 times the plasma level is usual, and ratios of over 100 can be attained by such measures as creation of an iodine lack, as by an iodide-deficient diet, or

*Symposium on Thyroid, read before a joint session, Sections on Medicine and Pathology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Department of Pharmacology, University of Alabama Medical Center, Birmingham, Ala.

Preparation of this paper was aided by grants from the Smith, Kline and French Foundation and the Committee on Growth, American Cancer Society.

FIG. 1



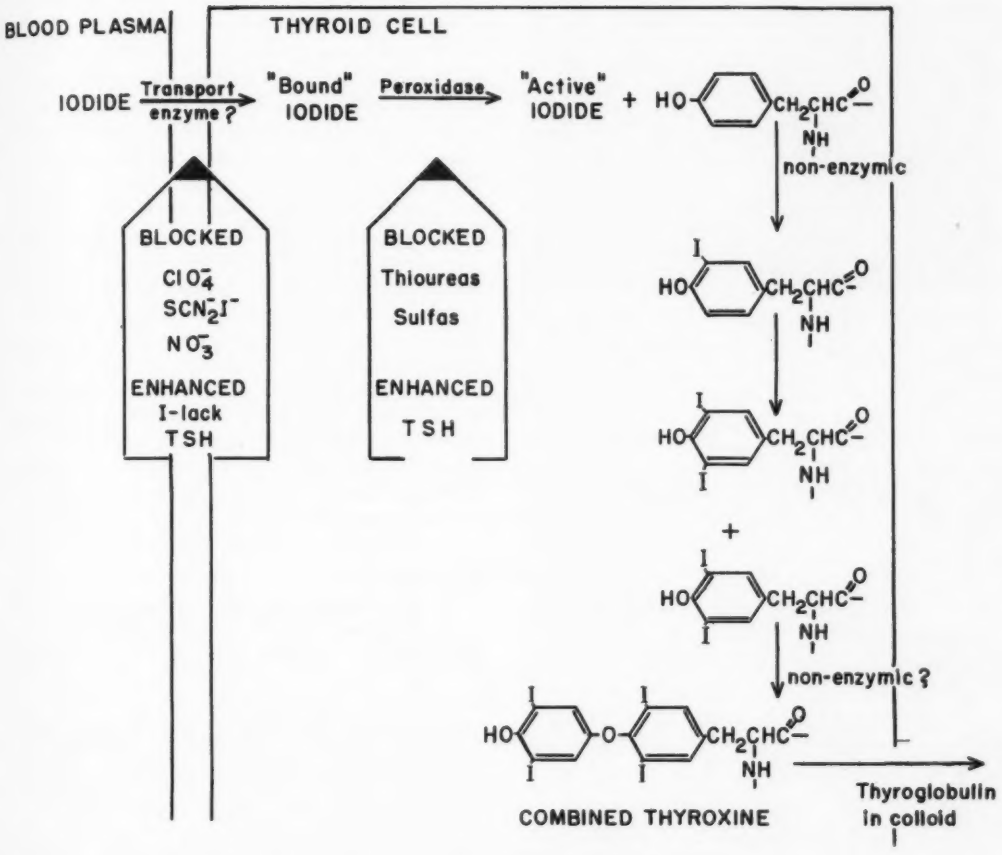
Physiology of the thyroid gland and its hormone.

increasing the levels of thyrotrophin (thyroid stimulating hormone, TSH).[2] It is also quite possible to explain this first step of iodide uptake on the basis of some enzyme-like process of binding of iodide inside the cell, perhaps by a specific protein. By lowering the intracellular level of freely diffusible iodide, the diffusion of iodide from blood plasma across the cell membrane may be greatly accelerated. The concept of a transport mechanism should be made broad enough to include provision of this type of binding complex inside the cell. Blocking and enhancing agents then may be considered to act on the complex either as it traverses the cell membrane or as it accumulates within the cell.

The bound iodide is next acted on by some type of peroxidase to produce an activated form considered by some workers as elemental iodine which attaches to tyrosine to form first monoiodotyrosine and then diiodotyrosine. Two diiodotyrosine molecules then come into sufficiently close approximation that an ether linkage is established between the benzene rings, with the elimination of one alanine side chain. The principal basis for concluding that these steps are nonenzymic is that thyroxine can be formed under strictly in vitro conditions from elemental iodine and protein,[3] or from iodide and protein in the presence of a peroxide-forming enzyme.[4] Evidence has been presented that copper catalysis may be important in the formation of monoiodotyrosine. As shown in figure 2, these reactions of iodination and combination to form thyroxine are carried out on tyrosine molecules combined in protein; there appears to be no action on added free tyrosine, monoiodotyrosine or diiodotyrosine.

Somewhere along this series of reactions, perhaps at the enzymic stage shown in the figure as peroxidase activation, a block can be imposed by three groups of compounds.[5] These are, (a) the thioureas, including thiouracil, methylthiouracil, propylthiouracil, methimazole, (b) the sulfas, none of which is as potent as the first group, and (c) polyphenols and aromatic amines, which again are not as potent. Methimazole and methyl- and propylthiouracil have a very useful function as

FIG 2



THYROID GLAND SYNTHESIS OF THYROXINE

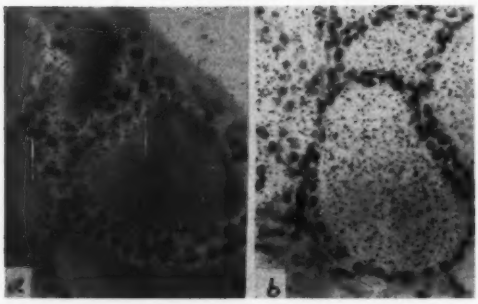
Synthesis of thyroxine by thyroid gland.

drugs which will control the hyperactive gland of the thyrotoxic patient, either on a long-term basis or for preoperative control of a patient on whom thyroidectomy is to be performed.

It should be realized that the agents shown as blocking iodide uptake by the gland (perchlorate, thiocyanate, etc.) are not sufficiently potent to be used for the complete control of hyperthyroidism. However, inadvertent blocking may result when ingestion of these compounds is continued over a long period of time, as when potassium thiocyanate was given for hypertension and when vegetables such as cabbage and turnip are featured in constantly large quantities in the diet. The thyroid hyperplasia from intensive cobalt therapy also belongs here. Historically, large amounts of iodide were introduced by Plummer as preoperative preparation, but even for that purpose, the more powerful thiouracils are now preferred.

Although the thiouracil and sulfa types of drug-blocking iodination has no direct blocking effect on iodide trapping, the iodide which has been picked up will not be retained more than a short time if it is not organically bound as iodotyrosine or iodothyronine. As Vanderlaan[1] has pointed out, iodide uptake, binding and organic synthesis by the thyroid gland seems to depend most intimately upon its own content of io-

FIG. 3

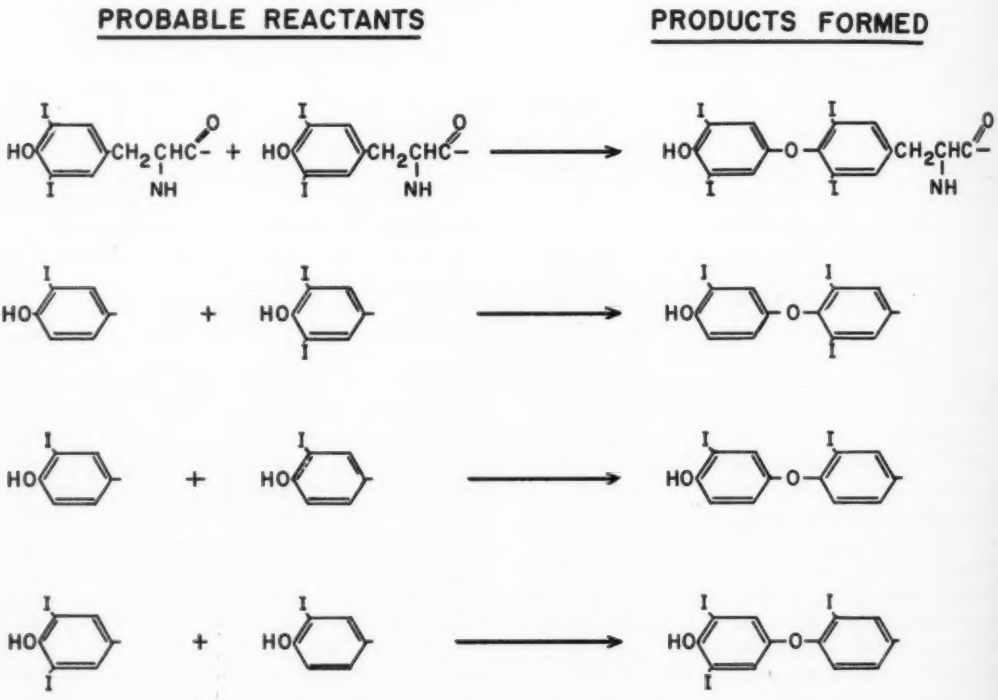


Autoradiograms of rat thyroid glands. (A) 1 hour and (B) 24 hours after radioactive iodide injection. From Leblond, C. P., and Gross, J.: Thyroglobulin Formation in the Thyroid Follicle Visualized by the "Coated Autograph" Technique, Endocrinology 43:306, 1948, courtesy of the authors and Charles C. Thomas, Publisher.

dine, especially organic. When the iodine stores are low, the gland appears avid, a situation seen in iodine deficiency goiter, and even more dramatically, in thyrotoxicosis. Such a relationship offers the best explanation for the enhanced iodine uptake without an increased circulating thyrotropin.

As iodination proceeds, the products seem to move, in protein form, into the thyroglobulin making up the colloid in the follicles. The progress of this material is shown in figure 3 (from Leblond and Gross[6]): at one hour (in the rat) after injection of radioactive iodide, the radioactivity is largely in the cells. By 24 hours, it is in the colloid, in the thyroglobulin. Two very practical applications of the phenomenon shown in the autoradiograms of figure 3 have been made in diagnosis and in therapy. Since the thyroid gland takes up such a large proportion of iodide administered to the body, radioactive iodide can be depended to go largely to the thyroid. Small amounts, about 1 to 100 microcuries, can be employed in a "tracer" or uptake study, and larger amounts, about 3 to 10 millicuries, for destruction of the glandular substance by internal ir-

FIG. 4



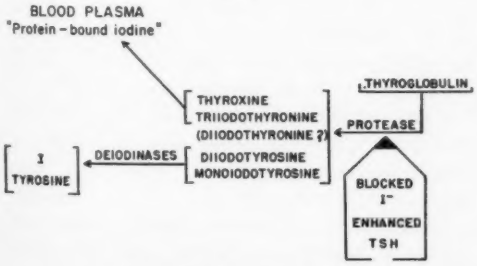
radiation, a sort of chemical thyroidectomy. In fact, under such circumstances as widespread metastases of functional thyroid carcinoma, radioiodine destruction is the only practical approach to elimination of this tissue. Other papers on the program will present these aspects in more detail.

Because of the tremendous amount of present interest in triiodothyronine as a more active form of the hormone than thyroxine, it is interesting to note that Roche and co-workers[7] have found a series of iodothyronines in the thyroid. As shown in figure 4, they consider these to arise from various combinations of mono- and diiodotyrosine. From above downwards, the products are thyroxine, 3,5,3'-triiodothyronine (the one commonly referred to as triiodothyronine or Trit), 3,3'-diiodothyronine, and 3,3',5'-triiodothyronine. The first two are now well known, but the third has only recently been reported to be as active as thyroxine itself. The fourth is much less active and will not be discussed further here.

Under the stimulation of TSH, the thyroglobulin protein in the colloid is broken down by a proteolytic enzyme[8] to yield amino acids, including the important iodinated forms shown in figure 5. Large quantities of iodide are able to block this proteolytic reaction. De-iodinating enzymes are present[9] probably in the thyroid cells, which rapidly break down mono- and diiodotyrosine but do not act on thyroxine or triiodothyronine. These two forms then diffuse out into the blood stream. The position of the 3,3'-diiodothyronine mentioned earlier is not clear, but since Roche has encountered this substance in the blood plasma, it probably is not attacked.

When physical disintegration of the gland takes place during therapy with I^{131}, large molecules are directly liberated similar to thyroglobulin, not ordinarily found in the blood plasma.[10]

FIG. 5



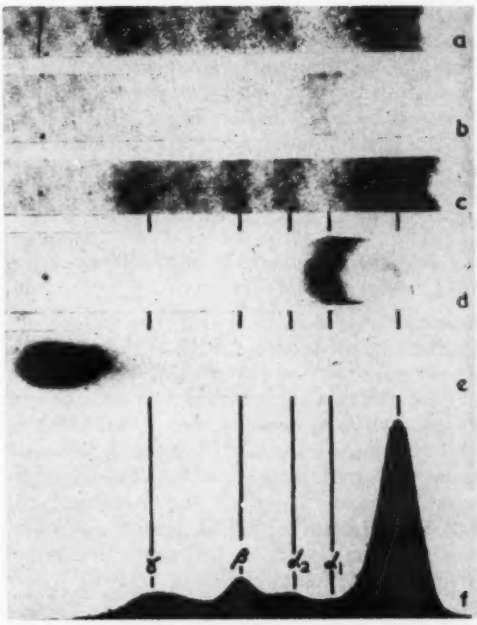
RELEASE OF THYROID HORMONE

II. Transport of Thyroid Hormone

In the course of the last 25 years, there have been many swings of opinion concerning the nature of the circulating thyroid hormone. During recent years, evidence has been overwhelming that the amino acid thyroxine is the principal circulating form, carried in some sort of loose combination with plasma proteins, especially α-globulins.[11] Figure 6 shows one of the earliest demonstrations of this thyroxine-protein combination.[12]

Triiodothyronine (Trit) added to plasma has been shown to be carried in a protein combination which is similar to but not as

FIG. 6



(A) Distribution of serum proteins after electrophoresis on paper of serum from a euthyroid subject five days after administration of NaI^{131} for treatment of thyroid carcinoma. (B) Autoradiogram of strip a; the principal area of serum radioactivity is between the a_1- and d_2- globulins. (C) Electrophoretic paper diagram of serum from an untreated euthyroid subject, to which radioactive thyroxine had been added prior to electrophoresis. Autoradiogram of strip c; radioactivity distribution is similar to that of b. (E) Autoradiogram of paper electrophoretic strip of the labeled thyroxine alone; little migration of thyroxine in the absence of protein is seen. (F) Electrophoretic pattern obtained in Tiselius apparatus of the serum shown in c enlarged so that the centers of the peaks for albumin and d-globulins would correspond with the equivalent bands on the paper. From Gordon, A. H., Gross, J., O'Connor, D., and Pitt-Rivers, R.: Nature of the Circulating Thyroid Hormone-Plasma Protein Complex, Nature 169:19, 1952, courtesy of the authors and Macmillan & Co., Ltd., Publisher.

firm as that with thyroxine.[13] This has also been demonstrated with regard to Trit of physiologic origin, although there is still disagreement about how consistently Trit is produced. The finding of a diiodothyronine in blood plasma is still too recent to allow a similar evaluation of this substance.

Here again, very great practical use has been made in diagnosis of the binding of thyroxine by plasma proteins in the plasma or serum protein-bound iodine test, also called PBI, serum precipitable iodine (SPI), organic-bound iodine, and serum hormonal iodine. Advantage is taken of the co-precipitation of thyroxine and protein to obtain the organic iodine free from inorganic which often is present in large enough quantities to spoil the value of the determination. Although a technically complicated procedure, determination of the PBI is not only practical, but is rapidly displacing the B.M.R., primarily due to the many subjective influences playing upon the latter. For a more dynamic evaluation the rate of incorporation of radioactive iodide into the PBI can be made, known as the PBI^{131}. This type of determination somewhat parallels that of iodide uptake by the thyroid at various time intervals. These procedures will also be discussed more fully in other papers.

III. Peripheral Activity of the Hormone in Tissues

Some of the many body functions which are affected by thyroxine are shown in table 1. These are so varied that it is almost essential to conclude that the hormone has some fundamental action on many tissues. This effect is probably one of stimulating energy turnover, or increasing the metabolic rate. This is prominent in the whole animal and in the patient, and is duplicated by the increased metabolic rate of many tissues excised from thyroxine-treated experimental animals, such as heart, skeletal muscle, diaphragm, liver, kidney, salivary gland, gastric mucosa and pancreas.[14] These particular structures are also altered in the reverse direction by thyroidectomy. Strangely enough, many other very important tissues show a metabolic rate not altered by thyroidectomy or thyroxine-injection, among which are brain, spleen, gonads of both sexes, accessory reproductive structures, lymph node, thymus and gastric smooth muscle.[15] From the point of view of mass of tissue involved, these tissues do not represent a major portion of the body, and their high degree of specialization may have removed their energy-obtaining mechanisms from thyroxine control.

TABLE 1

BODY FUNCTIONS ALTERED BY OR DEPENDENT UPON THYROID GLAND ACTIVITY

Metabolic rate, both basal and activity	Muscle physiology
Growth and development	Hematopoiesis
Many general aspects of fat, carbohydrate and protein metabolism	Renal function
Temperature sensitivity	Gastrointestinal tract activity
Vitamin requirements	Mobilization of bony calcium
Cardiovascular functions	Central nervous system activity
Reproductive function	Neuro-muscular function

The lack of metabolic response of the brain and reproductive structures raises the basic question of how the state of the thyroid can so greatly modify their functioning in vivo. There may be different explanations for each different tissue, such as the very high amount of energy apparently required to maintain the resting brain as compared to the extremely small added increment of energy required for a specific thought or motor process. We have been interested in enzymatic changes as related to thyroxine action and have found that the increase in succinoxidase produced by injected thyroxine in such tissues as heart, skeletal muscle, liver, and kidney, which respond metabolically, is matched by no consistent enzymatic change in brain, spleen and reproductive tissues.[16]

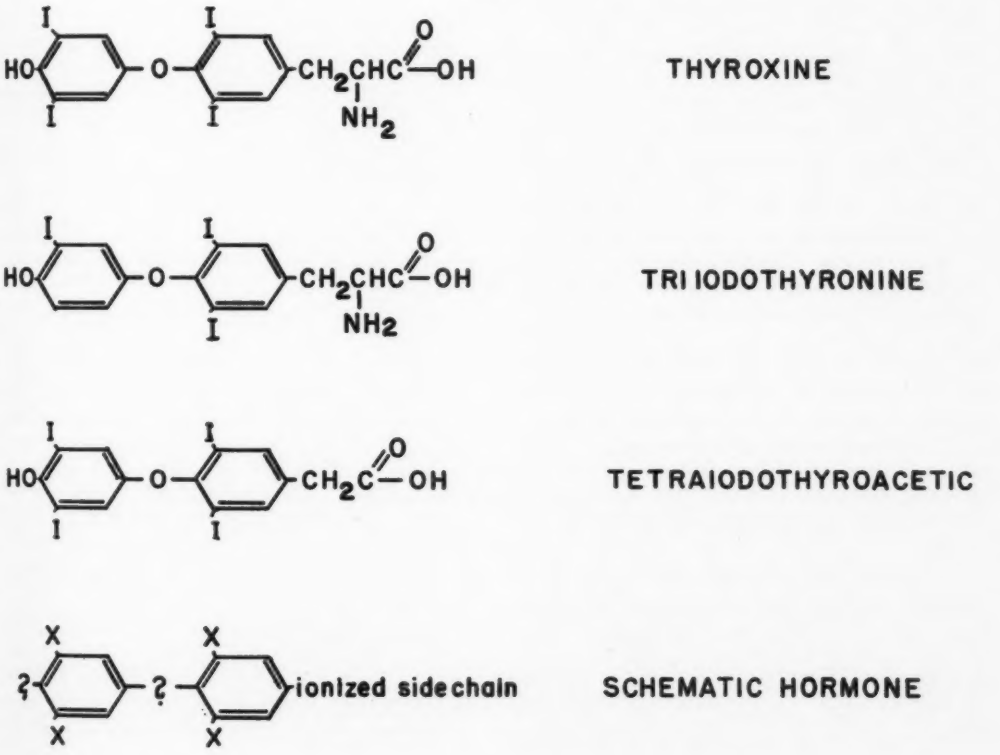
As part of the problem of finding out how the thyroid hormone produces its effects, there is much interest in determining the active form. Ever since Harington finally proved the structure of thyroxine in 1927, this compound has been the focus of attention. It has long been known that thyroxine, like desiccated thyroid substance, exhibited a delay before any metabolic response was apparent. It should not be implied that no changes whatever are going on during this period, indeed, quite the opposite is probably happening, but the effects on energy metabolism require many hours to be truly measurable. This is in marked contrast to a drug like dinitrophenol which is capable of a doubling of metabolic rate in a matter of minutes. In 1952, various workers demonstrated that 3,5,3'-triiodothyronine (Trit) could arise physiologically and was considerably more active than thyroxine itself.[17] Although at one time the claim was

made that Trit was active without any latent period, this has required modification to the extent that the latent period is shorter, but is still present. One current concept of thyroxine action is that it requires transformation into Trit before it can be active and that this accounts for the latent period for thyroxine. It has been shown that thyroxine certainly can be transformed in this way by some tissues, at least in small amounts. The time required for the partial de-iodination of thyroxine into Trit would not itself account for much of the latency.

Earlier this year, another pair of compounds was advanced as the active materials: thyroxine and Trit with the alanine amino acid sidechain diminished to acetic acid.[18] The structure is shown for tetraiodothyroacetic in figure 7; the triiodo analogue is easy to deduce. The report was that an immediate metabolic effect could be obtained after injection of these substances into a thyroidectomized animal, or after placing them in contact with excised tissue slices from such animals. Our laboratory has been very much interested in evaluating the metabolic activity of several different types of thyroxine-like compounds. We have found these iodothyroacetic analogues to be approximately as active as thyroxine and much less active than Trit. However, they do not exhibit any truly remarkable effects on tissue slices or on experimental animals. In other words, they produce changes similar to other structurally related compounds.

The entire series has great theoretical importance when one is considering the possible active portions of the thyroxine molecule. It

FIG. 7



POSSIBLE FORMS OF THE THYROID HORMONE

seems to establish that the portion of the schematized hormone formula shown in figure 7 shown as "Ionized side-chain" may not have a critical degree of specificity. The positioning of halogens on the benzene rings, shown as X's, is quite specific, with iodine much more active than bromine, chlorine or fluorine. The most active form of all thus far, as mentioned before, is Trit, with only one iodine on the outer benzene ring. The two question marks in the figure indicate portions of the structure which have not yet received enough study to warrant a definitive statement, except to say that the oxygen bridge between the two rings can be replaced by sulfur and still show some activity.

There remains the fascinating question of how the thyroid hormone acts; the following concept, admittedly somewhat arbitrary, is offered as a working hypothesis. Thyroxine is the principal circulating form of the hormone. It may be partially de-iodinated to Trit by the tissues in which it is active, but there is a whole series of synthetic compounds, any one of which can produce qualitatively the same action as either thyroxine or Trit without requiring transformation back and forth. The tissue changes resulting in metabolic stimulation build up over the course of several hours, during which time most of any administered hormone disappears from the body. This last situation strongly suggests that the hormone starts a chain of reactions and that it does not necessarily function as an integral part of all of these reactions. This activation could mean that the hormone causes some sort of intracellular rearrangement of enzymes and substrates so that their rate of functioning is increased. In the normal euthyroid individual, extremely small amounts of hormone are present all the time, and serve to maintain this postulated optimal interrelationship of enzymes and substrates.

The practicalities of this third portion of the thyroid hormone cycle are perhaps so obvious that one might lose sight of them. Even though the B.M.R. is becoming less important as a diagnostic evaluation, it still has a place. Therapeutically, replacement of deficient hormone production, no matter whether the cause be myxedema, excessive destruction of the gland or hypopituitarism, is essential to restoring the well-being of the patient. One step even further back from actual application is the realization of the importance of the hormone itself in producing the overburdening of the heart, the muscular tremors, the extreme nervousness and other facets of the entire syndrome of thyrotoxicosis.

Summary

This discussion has traced thyroid physiology and biochemistry in its tripartite aspects of (1) synthesis, storage and release of hormone; (2) circulation to the tissues of the body as protein-bound iodine; and (3) action of the hormone on the tissues. This over-all recapitulation has been for the purpose of laying a foundation for the several detailed expositions of thyroid and thyroid hormone function covered in these meetings.

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The Nonmalignant Thyroid Gland*

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THE PATHOLOGIC CHANGES IN THE THYROID PROVIDE a basis for classification and consideration of disease of the thyroid that extends beyond the purely morphologic character of the gland. It is the purpose of this presentation to summarize the features of certain lesions of the thyroid that are non-neoplastic in character. In the majority of instances these are goitrous and will be discussed under the following general headings: diffuse goiter, nodular goiter, and thyroiditis. The associated functional changes will be indicated.

Diffuse Goiter

Any enlargement of the thyroid gland that is manifested as a more or less uniform involvement, without apparent nodular change is commonly referred to as *diffuse goiter*. Such enlargements may be associated with hyperfunction of the gland and overproduction of thyroid hormone, with euthyroidism, or with hypofunction of variable degree.

Diffuse goiter with hyperthyroidism. Though the pathogenesis of this disorder is imperfectly known, the clinical symptoms have been recognized for many years and the basic pathologic changes are well defined. Of course, hyperfunction may occur in the absence of evident thyroid enlargement,[1] but the changes in both cases are similar. In hyperthyroidism the diffusely altered gland initially and typically is of dark-red color, meaty, and of obviously increased vascularity. The latter may be so severe as to be in effect a veritable arteriovenous aneurysm and the bruit which is commonly heard, is a result.

The basic changes occur in the follicles which are of irregular shape due to papillary-like infoldings of the epithelial layer. There is hypertrophy and hyperplasia of the epithelium,[2] and the cells may be several times normal height. Occasionally these goiters may be formed merely of closely packed small follicles without the infoldings, but the epithelial changes are otherwise the same. Colloid within the follicles is reduced, shown by a peripheral vacuolation and not infrequently by a marked general decrease so that the follicle contains but a little pink-staining coagulum. Foci of lymphocytes may be found in the stroma, and the latter may show an irregular increase. Vessels are engorged.

These histologic manifestations are representative of changes observed when there is undue activity of thyrotropic hormone which results in an increase in the activity and growth of the follicular cells and an acceleration in the formation and release of thyroid hormone. It has been suggested that the changes represent a hypersensitive gland[3] in association with an unusual production of thyrotropin but this has not been proved. Although thyrotropic hormone has not been demonstrated in the blood or urine of patients with Graves' disease, the histologic appearance of the gland certainly is compatible with an increased effect whether relative or actually due to hypersecretion of hormone.

In certain glands there may be considerable lymphocytic infiltration and fibrosis. These changes are reflected in a lower range of basal metabolic rate than otherwise present in Graves' disease, and are of practical importance because myxedema may follow surgical therapy.[4] Also there may be areas in which the follicles are distended with colloid and foci where the epithelium presents an oxyphilic character accompanied by a lymphocytic infiltration. These changes represent evidences of involutional change and so-called exhaustion.[2]

Changes in the basic appearance of diffuse goiter with hyperthyroidism occur after certain therapeutic procedures. Thus, the administration of iodides brings about reduction in the height of the cell and a reduction in enzymatic activity so that thyroid hormone may be stored. On section the gland presents follicles with lakes of deeply pink-staining col-

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loid and the epithelium is cuboidal or flat. Since individual follicles vary in reactivity,[5] the colloid and hyperplastic changes often are focal.

The use of thiouracil also alters the appearance of the follicle accentuating the hyperplasia by reducing formation of thyroid hormone. Thiouracil accomplishes this through its blocking effect on the oxidation of iodide, which results in the reduced formation of thyroid hormone and consequently less inhibition of thyrotropin production. If iodine is administered with the thiouracil there is focal reversion of follicles to a state of colloid distention. This is evidence that iodine may affect the height of the thyroid cell and its function even in the presence of a dysfunctioning follicle.[3]

The effect of radioiodine is damage of the thyroidal epithelium with decreased function. Early changes are desquamation of epithelium and a reduction in the height of the cell. Late changes consist of fibrosis and follicular atrophy and are shown by decreasing function over a period of months. In time the cells become oxyphilic in patches, increase in size so that they resemble Hürthle cells, and often have bizarre, large hyperchromatic nuclei.[6]

Simple diffuse goiter (endemic). Diffuse enlargement of the thyroid occurring in endemic areas is commonly considered due to the relative or absolute lack of iodine. It most frequently develops in persons less than 30 years of age; after a period of years the goiter assumes a nodular configuration. That iodine-lack is a factor has been recently substantiated by a survey by Hamwi, Williams, Whetstone and van Fossen.[7] They observed that the incidence of goiter in Ohio school children between the ages of 6 to 17 years, inclusive, today is only 4.0 per cent, whereas in 1925 the incidence was 32.3 per cent. Alterations of iodine in the diet have resulted from the use of iodized salt, the employment of fertilizers containing iodine, and the wider consumption of sea food.

Simple diffuse goiter is characterized by a uniform enlargement and a translucent appearance due to the storage of colloid in the distended follicles. Though the early phase of iodine insufficiency is manifested by hyperplasia, after a period of time the follicles involute and a stage of colloid storage begins. Since there is an inequality of both response and involution in various follicles, repetition of this process eventually leads to the formation of a nodular goiter. Histologically, the diffuse colloid goiter reveals large follicles formed by flat or cuboidal epithelium and filled with dense, homogeneous pink-staining masses of colloid.

Subiodidic goiter may result in cretinism (endemic), especially in Europe; such glands are generally of nodular type.

Congenital goiter. Approximately 70 cases of congenital goiter have been reported in the literature.[8] Some of these goiters are associated with sporadic cretinism, although the latter disorder is most often due to agenesis or atrophy of the thyroid. The familial character of sporadic goitrous cretinism is well recognized.[9] The thyroidal enlargement is considered to be due to an enzymatic defect in the thyroid cell which prevents the proper synthesis of thyroid hormone.[10] The protein-bound iodine values are exceedingly low, although the uptake of radioiodine may be high. In a recent study of a patient with sporadic cretinism, Stanbury, Kassenaar, Meijer, and Terpstra[11] found the protein-bound iodine value to be 0.5 micrograms per cent and were able to demonstrate mono- and diiodotyrosine, and some thyroxine, in the serum as well as in the thyroid. Grossly the congenital goiter is soft, fleshy, often pale and may be of nodular configuration. It has been described as high in position and frequently lying behind the pharynx and trachea.[8] The enlargement is due to a marked hyperplasia of the follicles, compensatory to the deficiency of thyroxine.

Diffuse hyperplasia due to drugs. The goiters associated with the administration of certain drugs result from an interference with the synthesis of thyroid hormone either through prevention of iodide concentration or a blocking effect on the utilization of iodide or iodine within the gland. Among the antibiotics, para-aminosalicylic acid and isoniazid produce goiters by a direct effect on the thyroid, blocking formation of thyroid hormone.[12] Thiocyanate and perchlorate prevent hormone formation by interference with the trapping of iodide. The thiourea compounds prevent oxidation of iodide to iodine. Since these substances may pass through the placental barrier, the fetal thyroid may be affected; administration of propylthiouracil

to the mother during gestation has been reported to produce goiter in the newborn.[13] Iodide when given in sufficiently large amount inhibits thyroid function and[14,15] thus is potentially a goitrogen.[16] Recently it has been reported that cobalt may be a goiter-producing agent.[17] Klinck[18] observed similar hyperplasia in the glands of young children who had not received cobalt therapy.

The morphologic features are hyperplasia of the epithelial cells, a reduction in the amount of colloid and an increased vascularity of the gland.

Dietary goiter. The effect of iodine lack is well known and has been briefly presented above in the discussion of subiodidic goiter. Direct goitrogenesis occurs from ingestion of foods containing compounds that prevent thyroxine formation. Goitrogenic compounds are present in members of the cabbage family, in rutabaga, white turnip, soya bean, and Brassica seed.[19,20] Goiters in man usually develop after raw vegetables, such as turnips, have been eaten for a period of months.[21] Frantz[15] reports one instance of an infant in which a goiter developed during the course of administration of soya-bean milk, and receded after this food had been omitted from the diet. Thyroidal enlargements due to foods containing goitrogens are rare; goiter is more rapidly produced in a thyrotoxic person.[21]

The pathologic changes in the gland are compensatory to diminished thyroid hormone production and are similar to those found in the diffuse hyperplasia associated with goitrogenic drugs.

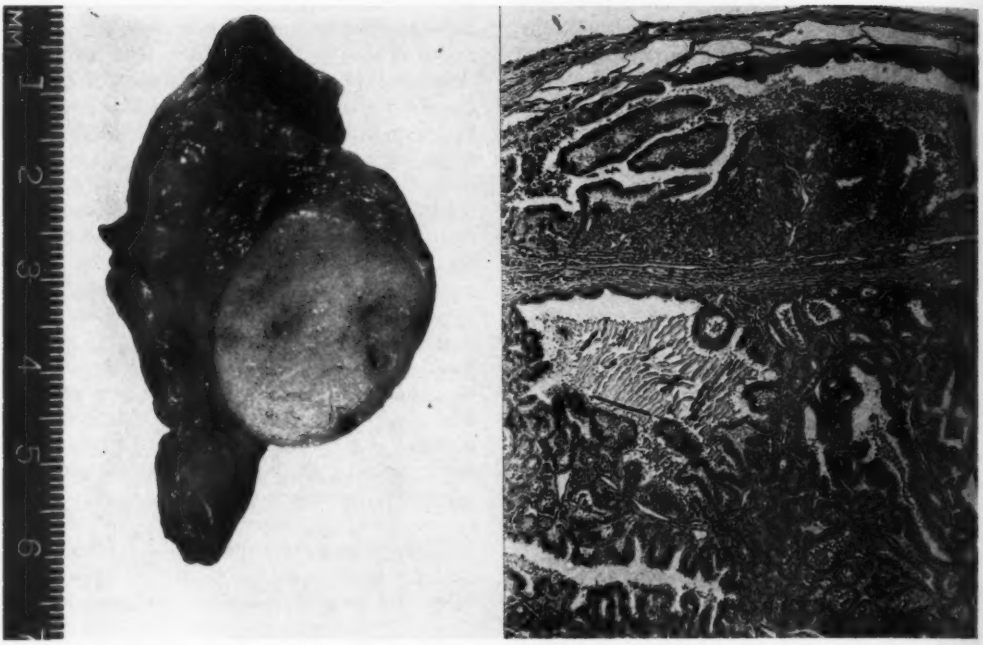
Nodular Goiter

Nodular goiter associated with hyperthyroidism and that of endemic type without hyperthyroidism may not be appreciably different morphologically, so that function cannot be determined accurately by histologic examination. The activity of thyroid nodules has been assessed by measurement of the height of the epithelium of the follicles and some have observed a correlation between function and the regular height of the epithelium. The nodular goiter with hyperthyroidism may show evidence of hyperplasia of follicles in the extranodular tissue. Activity in a thyroid nodule or other area may be most explicitly indicated by administration of radioiodine and preparation of radioautographs.[22] However, it is difficult to determine which of the nodular goiters is associated with hyperthyroidism since nodules with hyperfunction may occur in patients without hyperthyroidism.[22] In a recent study[23] of 90 patients having nodular goiters, 23 were found to be hyperthyroid with the serum precipitable iodine above 7 micrograms per cent, 65 per cent were euthyroid with values of 2.5 to 6.9 micrograms per cent. Many of the goiters revealing hyperfunction have been present for years. Grossly, whether hyperfunctioning or not, the glands reveal an irregular configuration either throughout the gland or in a portion. Occasionally the nodular change may be localized to a portion of a lobe so that it may be mistaken clinically for a solitary nodule. The sectioned surfaces reveal a variation in the size and prominence of the nodularity, some nodules being encapsulated and of adenomatous appearance, others appearing as mere enlargements of the thyroid lobules. Individual nodules vary from a typically follicular character to a structure of closed follicles and fetal appearance. Varying degrees of cystic change, fibrosis, old and recent hemorrhage, calcification or ossification may occur. Patches and bands of fibrosis and foci of lymphocytic infiltration are frequent. Occasionally there may be foci of oxyphilic epithelium in association with lymphocytic infiltration.

Nodular goiter is an aftermath of simple diffuse enlargement. Since the thyroid follicles vary individually in activity and in involutionary change with repeated onslaughts of hyperfunction and involution, focal enlargements occur due to increase in the number and size of follicles, and an increase in fibrous tissue. Thus, an irregularity in the size of thyroid lobules occurs, some becoming increasingly large and eventually assuming the contours of an adenoma. The fibrosis and focal lymphocytic change are a part of involution. After propylthiouracil therapy there may be an unusual degree of epithelial hyperplasia and a pseudoneoplastic appearance (Fig. 1).

The incidence of nodular goiter is paralleled by the age of the individual, being uncommon before the age of 30 years and increasing in frequency with succeeding years. In a series of thyroids studied at autopsy in the Cleveland area, 42 per cent of the adult

FIG. 1



A B

Nodular goiter after propylthiouracil therapy. (A) The nodular areas appear as white tumor-like masses. (B) Hyperplasia is so severe it produces a papillary appearance resembling papillary carcinoma. X60.

population were found to have one or more nodules in the thyroid.[24] Some of these were not associated with goitrous enlargement, but 8.8 per cent were classified as multinodular goiters (over 35 Gm.), with six or more nodules per gland. The incidence was slightly higher in women than in men. One and two-tenths per cent of single nodules were more than 2 cm. in diameter and presumably clinically recognizable.

Thyroiditis and Allied Disorders

The term *thyroiditis* has been rather loosely applied to any lesion of the thyroid in which there has been an infiltration of cells commonly associated with inflammation. Though such a designation may be applicable to those tissue reactions when certain of the "inflammatory" cells are involved, it is not so true of the lymphocyte since this cell may appear in tissues without the stimulus associated with inflammation.

A simplified classification is as follows:

I. Thyroiditis
   - A. Infectious
   - B. Physical
   - C. Granulomatous (subacute)
   - D. Riedel's
   - E. Nonspecific

II. Struma lymphomatosa

The incidental and nonspecific changes, whether they be fibrous or lymphocytic or both, and the lymphocytic infiltrations associated with toxic goiter, are not indications themselves of disease entities. Therefore, they will not receive separate consideration here.

Infectious thyroiditis. Under this term are included those diseases due to known infectional agents, bacterial and parasitic, in which the thyroid is primarily or prominently involved.

Acute infectious thyroiditis most often is caused by pyogenic bacteria and today is a rare illness. The more common agents are *Streptococcus hemolyticus, Micrococcus pyogenes aureus,* and pneumococcus. The disease usually occurs in association with infections

of the pharynx and upper respiratory tract. The lesions are of acute onset with fever, and the changes locally and distantly are those associated with such an acute infection. Suppurative and nonsuppurative types occur. In a recent publication, Altemeier[25] reports 10 cases occurring over a period of 15 years at the Cincinnati General Hospital.

In rare instances bacterial infection of the thyroid may be *chronic.* One organism causing such infection is *Salmonella typhosa,* which has been known to produce persistent abscess of the thyroid many years after the original typhoid infection.[26]

Echinococcosis is a parasitic disease affecting the thyroid[27] on rare occasions, the cysts being similar to those found elsewhere in the body.

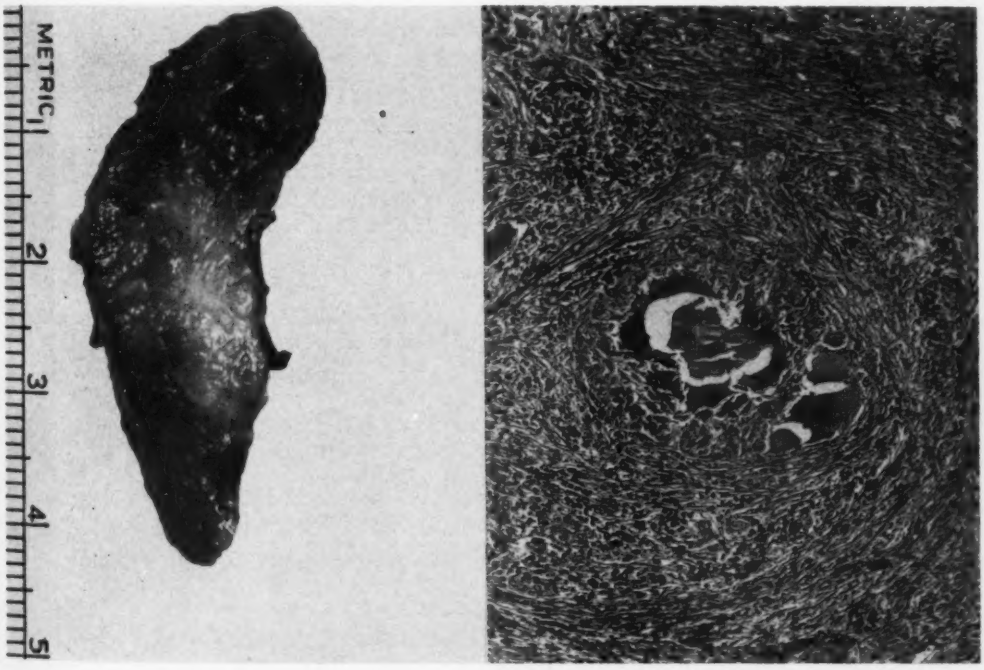
Syphilitic involvement is rare and may occur as a diffuse lesion or as a gumma.[28]

Thyroiditis due to physical agents. On rare occasions the thyroid is damaged by *trauma* either through direct injury with rupture of the gland or through introduction of an infectious agent.

Radioactive iodine now is a commonly used physical agent. In large dosage it produces an acute inflammatory reaction with edema of the gland and necrosis of epithelial elements;[29] and in smaller dosage, it may produce no changes or an increase in fibrous tissue. Late changes are oxyphilia of epithelial cells with foci of typical Hürthle cells, anisonucleosis, hyperchromatism, often associated with bizarre nuclear forms, variable amounts of fibrosis, and occasionally lymphocytic infiltration.[6] The biologic effects cannot always be predicted on the basis of dosage.[30] One of the characteristics of such radiation is the continued effect on the cell, even though the half-life of the isotope is short. In some cases decreasing function occurs for months after the I^{131} has been administered, and finally even hypothyroidism may result.

Granulomatous (subacute) thyroiditis. This is also known as *acute nonsuppurative thy-*

FIG. 2



A B

Granulomatous (subacute) thyroiditis. (A) Focus of whitish tissue replacing and blending with thyroid tissue. The capsule of the gland was intact. (B) Fibrosis and a granulomatous focus with foreign body giant cells about colloid. X100.

roiditis. If this term is used, care must be taken to distinguish it from acute thyroiditis of bacterial origin. Although the cause of the disease is not known a viral etiology is suspected.

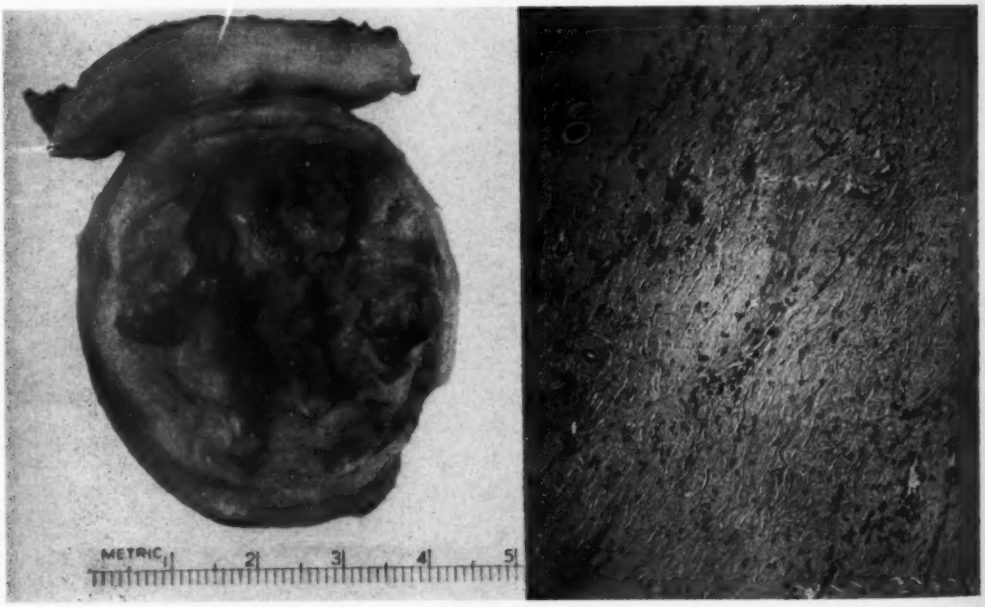
The basic lesion is an injury to the follicle cells. It often appears in one portion of the thyroid, and then migrates to involve other areas of the thyroid so that the term *creeping thyroiditis* has been applied. Characteristically, a firm, tender focus is present in one or both lobes of the gland. Section of the thyroid reveals a white, fibrous area blending with normal-appearing thyroid tissue (Fig. 2, A). However, uptake of radioiodine is markedly reduced,[31,32] so that actual alteration of function of the thyroid epithelium must be beyond that observable in the pathologic specimen.

There may be symptoms of hyperthyroidism since injury of the follicular epithelium permits direct release of thyroid hormone. The thyroid contains sufficient preformed hormone to last about two months. Recovery occurs frequently before this reserve is exhausted, so that symptoms of hypothyroidism are uncommon.

The histologic feature characterizing the lesion as granulomatous, is the focal collection of histiocytes and foreign body giant cells throughout the involved area. On occasion, lakes of colloid may be found surrounded by the granulomatous reaction (Fig. 2, B). This is most often due to exposure of the colloid to stromal cells through loss of the follicular epithelium rather than to actual direct extrusion of the colloid. Recently it has been suggested that the foreign body reaction may be due to the presence of a crystalline material (calcium oxalate monohydrate) in the colloid.[33] However, these crystals occur in the thyroid without such a granulomatous reaction even in the presence of follicular injury.

The diagnosis of the illness, though usually possible clinically, occasionally may be difficult because of atypical symptoms. In these instances, needle biopsy of the thyroid has been helpful in distinguishing the condition from struma lymphomatosa, diffuse goiter

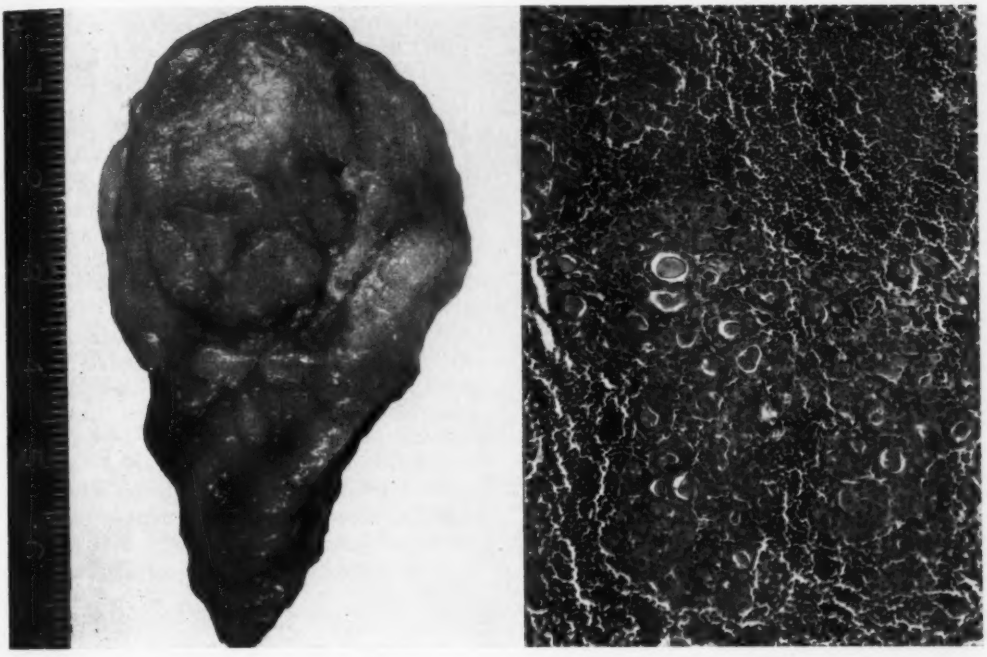
FIG. 3



A B

Struma fibrosa (Riedel's thyroiditis). (A) Surgical specimen, reconstructed, showing a cap of dense white tissue incorporating thyroid tissue and muscle and overlying a cystic adenoma. The thyroid capsule was obliterated by the fibrous mass. (B) Hyaline fibrous tissue and a few atrophic follicles replacing the normal thyroid tissue; slight inflammatory infiltrate. X100.

FIG. 4



A B

Struma lymphomatosa (Hashimoto type). (A) Thyroid lobe with nodular configuration and bulging gray-white cut surface. (B) Typically small follicles formed by epithelial cells of larger size than usual and separated by a dense lymphocytic infiltrate. The epithelium was of oxyphilic character. Plasma cells were present in areas. X100.

with hyperthyroidism and other disorders.

The disease is self-limited, but the course may be prolonged; cortisone is favored as a therapeutic agent.[34]

Struma fibrosa (Riedel). This rare disorder is commonly known as *Riedel's thyroiditis,* having been first described by Riedel in 1896.[35] The term *fibrous invasive thyroiditis* has been suggested as a diagnostic term, and is accurately descriptive, since a simple fibrosis is not characteristic of the disease. The lesion most often is present in one thyroid lobe, though there may be bilateral involvement. The gland is not very large but pressure symptoms occasionally may be severe. The degree of tracheal and even esophageal obstruction is due to violation of the capsule of the thyroid by the fibrous proliferation characteristic of the disease, and to invasion of the soft tissues adjoining the thyroid by the fibrous mass. Thus, the thyroid, partly replaced by the white, extremely hard, fibrous tissue, becomes densely incorporated with the adjoining tissues and can be removed only in portions since planes of dissection are lost. In approximately two thirds of the cases in one series,[36] an adenoma was present within the gland (Fig. 3, A). This makes it feasible in some instances to expose the adenoma by removal of a cap of tissue, enucleate it, and thus decompress the gland. The adenoma usually is of simple follicular character and may exhibit cystic changes, fibrosis and calcification. Occasionally, the adenoma may be so densely incorporated in the mass that it must be removed piecemeal. Since the process usually is only present in a portion of the thyroid and abundant functioning thyroid remains, function is retained and the patient is generally euthyroid.

Histologically, the thyroid tissue in the involved area is entirely replaced, or replaced except for a few isolated small follicles, by connective tissue which is often of hyaline character (Fig. 3, B). An infiltration, generally sparse, is present, comprised of lympho-

cytes, plasma cells, and sometimes neutrophils. The fibroplasia may be of hypercellular character and extend in almost neoplastic character into adjoining muscle. The adenoma, except for its outermost rim, generally shows little involvement by the fibrosing or inflammatory process.

The lesion is benign, but death may result from the severe tracheal compression.

Struma lymphomatosa. The disorder commonly known as struma lymphomatosa or Hashimoto's disease was first described by Hashimoto in 1912.[37] It occurs principally in women and rarely in men and children; it is commonest in the fifth and sixth decades with an average age between 40 and 45 years.[38] The entire gland usually is affected, although involvement of the pyramidal lobe or of a nodular gland may simulate a localized lesion, even a solitary adenoma.

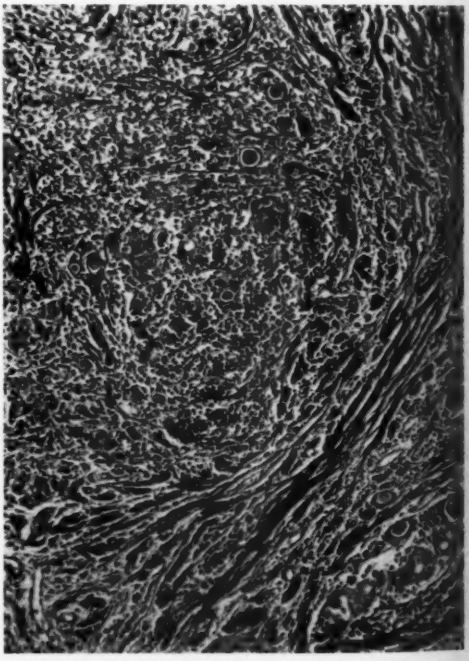
The symptoms usually are associated with the appearance of a goiter; though a certain amount of hypothyroidism may be present, it most often is of compensated type. However, on removal of thyroid tissue as in subtotal thyroidectomy, decompensation is common and even myxedema may occur. Therefore, it is well to recognize the disease clinically without operation, and the use of needle biopsy has been found effective in this respect.

Recently, Dailey, Lindsay and Skahen[39] have reported a high incidence (17.7 per cent) of carcinoma, usually of a low grade of malignancy, in glands with struma lymphomatosa. One-fifth of the carcinomas were not suspected clinically and such an occult group was of similar frequency in carcinomatous glands with or without Hashimoto's disease.

The thyroid is usually enlarged to 2 to 5 times normal size. The capsule, though it may be slightly thickened and slightly adherent to adjacent structures, is intact. On section, the tissue is commonly of firm consistence, lobulated with a slightly bulging surface, and ochre or white in color (Fig. 4, A). A fibrous variant[40] occasionally is found in which the tissue is very hard and the cut surface flat and white. Even in this form, however, the capsule of the gland is not violated by the disease.

Struma lymphomatosa of the *Hashimoto type* (Fig. 4, B) is characterized by an oxyphilic change in the epithelial cells[41-43] over broad areas of the gland and not infrequently the entire gland. This diffuseness of alteration is a distinguishing feature from nonspecific involutionary changes. Characteristically, the follicles are small, round, ranging from 50 to 75 microns in diameter; occasionally, however, they may be of medium and even large size, and show infoldings of the epithelial layer. Infiltrations of lymphocytes, and not infrequently of plasma cells, occur characteristically over broad areas, separating individual follicles. Large lymph nodules are commonly present. The outlines of the original lobulations of the thyroid are evident, even though masked by fibrosis, enlargement of the lobules and at times a relative reduction in the number of follicles. Colloid often is dense, intensely staining, and with minimal marginal scalloping.[44] In some follicular lumens there may be marked reduction of colloid and a collection of histiocytes. Though a few intrafollicular giant cells may be found, a granulomatous reaction, as seen in subacute thyroiditis, never is present. In a few fibrous glands, the so-called fibrous variant, there is

FIG. 5



Struma lymphomatosa (Hashimoto type), fibrous variant. Bands of dense fibrous tissue separate lobules of sparse, atrophic follicles isolated by a dense lymphocytic infiltrate. The epithelium was of oxyphilic type. The capsule of the gland was intact. X70.

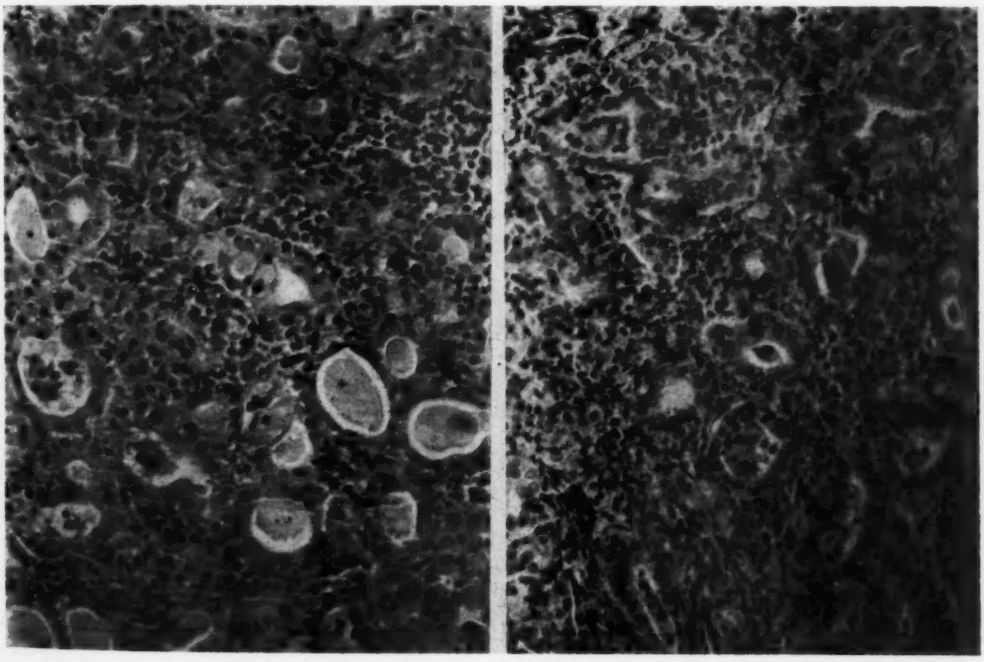
an abundance of hyaline fibrous tissue (Fig. 5).

In addition to the classic Hashimoto type described above, several authors have recognized a lesion of the thyroid closely resembling it pathologically, but occurring in a younger age group. This has been referred to as *lymphoid* or *lymphocytic thyroiditis*[45,46] and as *lymphocytic thyroiditis (Hashimoto's disease)*.[47] The lesion is not inflammatory and such terms are accordingly objectionable. Because oxyphilia of the epithelium is not so prominent a feature as in typical Hashimoto's struma (Fig. 6), the lesion might be designated as a nonoxyphilic or a slightly oxyphilic variant of struma lymphomatosa. Since there also is a common tendency toward infolding of the epithelial layer of the follicles it could also be designated as a hyperplastic variant. Most often the lesion occurs in adolescents of both sexes or in young women, although the disease has been observed in those in the fifth decade. It is usually manifested as a simple swelling of the thyroid and has on several occasions made its appearance soon after parturition.[48,49] The thyroid failure present is most always compensated and the patient euthyroid. Clinically the thyroid enlargement may be confused with simple colloid goiter. Needle biopsy has been a valuable aid in the differential diagnosis.

The gland is enlarged diffusely and the contours are variably smooth, or lobulated. On section, the tissue is commonly gray or yellowish white, at times almost sarcomatous in appearance. The thyroidal capsule is thin and intact.

Microscopically, the follicles typically are of normal or slightly larger than normal size, and the epithelium is columnar, often with infoldings of the epithelial layer and a wavy follicular contour. Oxyphilia may be absent, focal, or present diffusely in slight amount. The follicles are separated by masses of lymphocytes, often with prominent lymph follicles, and occasionally with intermingled

FIG. 6



A B

Two variants of struma lymphomatosa, each with a marked lymphocytic infiltrate and with histiocytes in follicular lumens. (A) Follicles of fairly round contour with large epithelial cells. The epithelium was oxyphilic. X240. (B) Follicles of cuboidal or low columnar epithelium with some infoldings of the epithelial layer. The epithelium was nonoxyphilic. X240.

plasma cells. The lymph nodules usually are not evident in specimens obtained by needle biopsy. Fibrosis of a degree seen in the Hashimoto type is not ordinarily encountered in this variant. The follicle lumens most often contain little or no colloid; histiocytes and a few foreign body giant cells are often found, nearly filling the otherwise almost empty follicle lumens. Occasionally, foci of follicles distended by colloid may be seen.

Recently there have been several interesting developments in the study of struma lymphomatosa, indicating that primary follicular failure is a common factor in these two variants. Gribetz and associates[47] noted in their juvenile cases that the protein-bound iodine might be elevated but the butanol-extractable fraction was low, and the patient revealed no hyperthyroidism. They projected the possibility that the disorder of the thyroid was compensatory and a result of disordered synthesis and release of thyroid hormone and hence a lack of the usual control of thyrotropin formation. More recently, Skillern and associates[49] studied a series of patients with struma lymphomatosa representing both variants, and found similar qualities so far as thyroid function and certain biochemical aspects were concerned. In the 36 patients in their series, three-fourths were clinically euthyroid (compensated thyroid failure). The basal metabolic rate was minus 15 per cent or below in two-thirds of the patients. The radioiodine uptake was low to high and, most important, a stimulation test with thyrotropic hormone[50] failed to increase the rate of thyroidal raidioiodine uptake *in all* patients. Cholesterol values were not distinctive, ranging from high to low. The protein-bound iodine (PBI) values were usually low-normal. The butanol-extractable fractions (BEPI) afforded more useful measure of thyroid hormone deficiency, being unusually low or low-normal, but still were not definitive. However, the values representing differences between the PBI and BEPI were higher than usual, more nearly averaging 2 micrograms per cent than the 0.7 microgram commonly found. Previously, Cooke and Wilder[51] and Cooke and Luxton[52] observed a paretic type of colloidal gold curves in the sera of patients with struma lymphomatosa. Thymol turbidity and flocculation tests usually were parallel with the colloidal gold regarding abnormality. In the series of Skillern and associates, the serum colloidal gold gave a positive test, i.e., a paretic curve, in about three-fourths of the patients. Correlating electrophoretic fractionation of the plasma proteins revealed that the albumin was usually decreased and the gamma globulin increased. The abnormal colloidal gold curve correlated with the elevated gamma globulin and lowered serum albumin.

The physiologic and biochemical characteristics indicate that the basic lesion is a primary failure of the thyroid follicles, with a certain degree of deficiency of thyroxin production and a resultant increase in endogenous thyrotropin production. The cells retain a part of their usual responses, undergoing hyperplasia to produce a goiter, and concentrating iodide, often quite well. That the latter function proceeds at a maximal rate for a given gland is shown by the insignificant response to the thyrotropin-stimulation test. The similarity of the findings in the goiters of typical Hashimoto type and those with the non- or slightly oxyphilic follicles suggests that they are basically the same and are morphologic variants of the one group, struma lymphomatosa. The several variations in the degree of oxyphilia of the epithelium make it difficult in some instances to differentiate precisely between the two types, even histopathologically.

Therapeutic procedures to be effective in relieving stress on the thyroid, must correct the thyroxin deficiency and thus counteract thyrotropin production. This may be accomplished by administration of desiccated thyroid[53] (usually 3 grains daily), a procedure which commonly produces a decrease in the size of the goiter and tends to correct the abnormal electrophoretic pattern.

Primary Idiopathic Adult Myxedema

The thyroid in this disorder typically is atrophic, being formed of fibrous tissue, a few diminutive lobules of small follicles and collections of lymphocytes and a few plasma cells.[54] The gland in some cases may be palpable but is not enlarged.[55] The epithelium is mostly of oxyphilic character, resembling that of the Hashimoto type of struma lymphomatosa. That the follicular failure is prac-

tically complete is evidenced by features of atrophy, or lack of hyperplasia, and the occurrence of myxedema.

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Discussion (Abstract)

Question: The question is not directed at anyone in particular and is as follows: Is there any increasing incidence of Hashimoto's disease and also subacute thyroiditis? There seems to be such an increase in the Houston area.

Dr. Hazard: Accurate figures are somewhat difficult to obtain. We believe there is an increase; 36 of the needle biopsies which we studied were collected in just a little over nine months, and that is a considerable incidence of struma lymphomatosa. It is hard for me to judge from the surgical pathologic figures because I do not see struma lymphomatosa at operation any more, and I practically never see thyroid tissue with subacute thyroiditis since most of the patients are treated medically. I am told that subacute thyroiditis is certainly not an uncommon disorder in so far as our clinical services are concerned. Whether

it be greater recognition or not, I do not know. Certainly, as I said earlier, on occasions in the past struma lymphomatosa has been mistaken for simple colloid goiter. However, because of the fact these patients do not do well with iodine therapy, more recently needle biopsy has been done to insure greater accuracy in diagnosis. It is our belief that there has been an increase in struma lymphomatosa and that subacute thyroiditis also is either increasing or else is better recognized.

Thyroid Hyperplasia: Report of a Case in an Infant Treated with Cobalt*

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COBALT SALTS ARE FREQUENTLY USED in the therapy of anemia. Quilligan[1] has emphasized the beneficial therapeutic effect of cobalt in the anemia of infancy. One of the group of patients discussed by him succumbed as a consequence of thyroid enlargement. The purpose of this paper is to report this case in detail, with emphasis upon the pathologic findings in the thyroid.

Report of Case

A 4 month old white male infant was admitted to Bradford Hospital, Dallas, with the symptoms of coughing, wheezing and "respiratory obstruction" of 3 weeks duration. Prior to admission the infant had been treated with antibiotics for an upper respiratory infection manifested by a low-grade fever, coughing and wheezing. Three days before admission the infant had a "choking spell" which was described as an inability to cough or clear the posterior part of the pharynx. He showed no cyanosis during this episode of apparent respiratory obstruction. Following this attack he improved but continued to wheeze and cough intermittently.

On the day of admission, while nursing, the infant became cyanotic, and then had apnea for a period of time. He was immediately given artificial respiration with dislodgement of a mucous plug, after which the breathing became normal and the cyanosis disappeared.

Past History. The infant was born prematurely, at 7 months of gestation, and weighed 3 pounds, 1 ounce at birth. (The mother threatened to abort at the end of the third month of pregnancy.) Following 25 hours of labor, the mother was delivered. The baby was in cephalic presentation and had a good cry. There was no history of cyanosis at this time. He remained in the premature nursery for 6 weeks and was discharged with a weight of 5 pounds, 1 ounce. In the intervening three and a half months the infant did well at home and was relatively free of any complaints until 3 weeks before admission.

During his stay in the premature nursery he was treated daily with 10 drops (0.6 ml.) of Roncovite. This quantity of Roncovite contains 40 mg. cobaltous chloride and 75 mg. ferrous sulfate. He was fed Similac and gained weight progressively. Karo syrup was later added because of constipation. The appetite was described as good.

Family History. Mother and father were in good health. There were no siblings.

Physical Examination. Temperature 98.4°, pulse 160, weight 10 pounds, 4 ounces. Upon arrival at the hospital the infant did not appear to be in respiratory distress, but was placed in an oxygen tent. Examination of the head, eyes, ears, nose, throat and skin revealed no unusual findings. The facies were normal. Respiration was rapid but normal in depth. Auscultation revealed harsh breath sounds throughout both lung fields but no rales were detected. The heart rate was 160 per minute, the rhythm was regular, the size normal, and no murmurs were heard. The abdomen was soft, no masses were palpable and the extremities were normal. Neurologic examination was normal except for slight hyperactivity of all reflexes.

Laboratory Findings. Serum calcium, 12.1 mg. per 100 ml.; Hgb., 14.7 Gm.; erythrocytes, 5,120,000; leukocytes, 15,100; differential count, 71 polymorphonuclear leukocytes, 25 lymphocytes, 1 monocyte, 3 eosinophils; urine, specific gravity 1,005, reaction 8.5, no albumin or sugar, 1 or 2 red blood cells per high power field.

Progress. One day after admission the infant developed an obstructive type of breathing with marked sternal retraction and cyanosis. He was promptly given oxygen. Milk was aspirated from the mouth and pharynx. In a short time his color improved but the labored respiration continued for about 15 minutes, after which it gradually subsided to a more nearly normal rate. Food was subsequently withheld. The infant had another similar attack later the same day.

Laryngoscopy revealed striking edema of the mucous membranes of the cricoid and arytenoid cartilages, the aryepiglottic folds and the epiglottis. It was believed that the right vocal cord was paralyzed. There

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was no edema of the vocal cords. Under anesthesia the patient's thyroid gland was easily palpable. The gland was enlarged 4 to 5 times normal size and was thought to be somewhat nodular, the right lobe being larger than the left. The consistency of the gland was firm, almost hard.

Following laryngoscopy the infant developed laryngeal spasm and it was necessary to intubate the trachea with a plastic endotracheal tube which was left in about 30 minutes. ACTH and adrenalin were administered. With subsequent improvement in the respiratory difficulty, the tube was removed. Despite administration of oxygen the infant continued to have periods of apnea and cyanosis. A tracheotomy was performed on the eighth hospital day. At the time of operation the isthmus of the thyroid gland was removed exposing the trachea. It was felt there was considerable inflammatory tissue between the trachea and thyroid which was thought to be typical of thyroiditis. Following tracheotomy the infant's obstruction to breathing improved remarkably. On the twenty-sixth day of hospitalization the infant had periods of cyanosis followed by apnea, and ultimately died on this date. Death was thought to have been caused by obstruction of the upper airway owing to collection of excessive mucus.

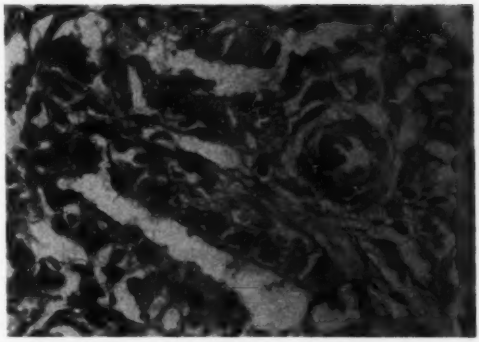
Autopsy Findings. There was an incision 6 by 5 mm. at the level of the fourth tracheal ring with an opening into the trachea. The trachea contained a small quantity of thick tenacious material. Microscopic examination revealed chronic tracheitis with squamous metaplasia. The lungs occupied about 85 per cent of their respective pleural cavities. They were pale pink and contained air except for moderate atelectasis of the lower lobes. Microscopic examination revealed atelectasis and focal pulmonary edema. The heart was normal grossly and microscopically.

The thyroid gland, which weighed 21 Gm., was grossly enlarged, smooth and reddish-brown. The isthmus had been previously excised to permit a tracheotomy. The thyroid was firmly adhered to the trachea. There was no detectable lymph node enlargement.

Microscopic examination of the thyroid gland showed diffuse atypical pseudoneoplastic hyperplasia. The normal interstitial fibrous tissue of the gland was accentuated, producing a finely nodular compartmentation of the gland (Fig. 1). The acini were virtually devoid of colloid and their lumens were reduced. The epithelial cells were atypical in appearance and varied in shape from oval to tall cuboidal or columnar (Fig. 2). They contained scant eosinophilic cytoplasm and had large round or oval hyperchromatic nuclei with prominent nucleoli and an increased amount of vesicular chromatin. No mitotic figures were encountered. The acini were regularly distributed and no vascular invasion or capsular penetration was seen. This appearance was uniform throughout the entire gland. The remaining endocrine glands were grossly and microscopically normal.

FIG. 1

FIG. 2



Comment

This form of thyroid hyperplasia in association with cobalt therapy has not been adequately reported in the literature. Dr. W. A. Meissner[2] of Boston and Dr. R. T. Gross[3] of San Francisco have indicated to us in a personal communication that they have seen a few similar cases, and Drs. R. T. Gross, J. P. Kriss and T. H. Spaet[3] reported similar findings at the American Pediatric Society Meeting, May 19, 1954. This material has been published in the *Journal of the American Medical Association* of January 8, 1955. In view of the pseudoneoplastic aspect of the lesion it is interesting that Heath[4] reported that the addition of cobalt to tissue cultures of chick fibroblasts will produce nucleolar abnormalities and that intramuscular injections of cobalt in the rat will produce malignant tumors.

Summary

An unusual form of hyperplasia of the thyroid gland was encountered in an infant treated with cobalt. A causal relationship between the therapy and the thyroid hyperplasia is postulated.

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The Morphologic Variations of Goiter in the Lower Rio Grande Valley*

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FOR SOME TIME there has been a feeling in the Lower Rio Grande Valley that there is a variation from the usual in the classification of goiter in our area. This opinon has been expressed by a number of physicians in several communities of this area as well as from other areas in southeastern Texas.

A review of the last 63 consecutive cases in which the patients have had a thyroidectomy in Brownsville, Texas, revealed 18 instances of diffuse goiter, 14 of nodular goiter, 6 of struma lymphomatosa, 22 of various follicular adenomas, some of which may actually have been nodular goiter, one papillary adenoma and 2 papillary carcinomas (Table 1). These figures agree in general with the findings of others, but our attention was drawn to the cases of struma lymphomatosa which show an incidence higher than in most reports. Many large collections of cases of thyroid disease have been found in the recent literature with struma lymphomatosa comprising from 0.31 to 3.3 per cent.[1-6] Chesky, Dreese and Helwig[7] report an incidence of 7.1 per cent struma lymphomatosa in 2,031 instances of thyroid disease in Halstead, Kansas. Kisner[8] found an incidence of 8.16 per cent in Natchez, Mississippi. The incidence in our small series is 9.5 per cent.

Of our patients all were women whose ages ranged from 34 to 50 years. Four were Anglo-American and two Latin-American. Since the population in Brownsville is predominately Latin-American one might expect more cases in that group, but we believe many of the Latin-American women are content to live with a goiter while probably more of the Anglo-American women will have them removed.

Struma lymphomatosa was first described by Hashimoto[9] in 1912. Several extensive articles defining the disease clinically and pathologically and reviewing the literature have appeared recently.[1-7,10-13] Our criteria for diagnosis of struma lymphomatosa conform to those generally described. Grossly the gland is firm and moderately enlarged in most cases. There is a definite lobular pattern and the cut surfaces are orange-gray. The capsular surface is lobulated and even nodular in some cases. Microscopically there is diffuse lymphocytic infiltration with germinal centers. There is atrophy of the follicular epithelium with a rather prominent eosinophilia of the abundant cytoplasm. Coupled with the gross and microscopic features the clinical findings should be considered in the diagnosis. The patients are women who have moderate goiters

TABLE 1

DIAGNOSES IN 63 CASES OF GOITER

	Number	*Per Cent*
Diffuse goiter		
Nontoxic	4	6.3
Toxic	14	22.2
Nodular goiter		
Nontoxic	8	12.7
Toxic	6	9.5
Struma lymphomatosa	6	9.5
Follicular adenoma	22	35
Papillary adenoma	1	1.6
Papillary carcinoma	2	3.2
Total	63	100.0

*Symposium on Thyroid, read before a joint session, Sections on Medicine and Pathology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

usually without discrete nodules. There may be symptoms of pressure but no thyrotoxic symptoms are present, and a hypothyroid state is common. The onset of the goiter and symptoms is insidious and slowly progressive.

The histogenesis of the disease has been obscure but there have been recent additions to our information. Furr and Crile[11] stated that "The cause of lymphocytic infiltrate may be the result of an increase in thyroid-stimulating hormone production by the pituitary, or a decrease in the production of potent lymphoid-moderating hormones."

Chesky, Dreese and Helwig[7] described a difference from the normal in the shape and size of the colloid particles observed under the electron microscope. They observed active colloidophagy of the altered colloid by macrophages which re-entered the stroma where, upon disintegration, the colloid elicited a lymphocytic response. The increased colloidophagy in lymphadenoid goiter, they believe, is the result of increased thyrotropic hormone.

Gribetz, Talbot and Crawford[14] studied six cases of lymphocytic thyroiditis in young girls with protein-bound iodine and butanol extractable iodine determinations. Their findings indicat ethat perhaps the protein-bound iodine in these cases has a larger portion of noncalorigenic substances than in normal thyroids.

In 1929, McCarrison[15] produced lymphadenoid goiter in rats with a diet containing iodine and deficient in vitamins. While studying the effects of prolonged administration of thiouracil to rats, Clausen[16] noted that 25 per cent of his animals exhibited a chronic thyroiditis of the Hashimoto type. This is the same percentage of occurrence reported by McCarrison. Clausen feels that perhaps instead of a vitamin deficient diet being the causative factor some goitrogenic substance may have been present.

Some studies have shown a relationship between lymphatic tissue and thyroxin. Turley and Richter[17] gave a lymphocytogenic drug along with fatal doses of thyroxin to guinea pigs and prevented death. Rawson, Sterne and Aub[18] demonstrated inactivation of the thyroid-stimulating hormone by both thyroid tissue and lymphatic tissue. These findings have been interpreted as indicating that a lymphocytic response might be a defense mechanism to thyroxin and thyroid-stimulating hormone.

Since many of the older etiologic theories in regard to struma lymphomatosa, such as an infectious origin, ovarian disturbance,[6] or the end result of a toxic diffuse goiter, seemingly have not been substantiated, the concept of Statland, Wasserman and Vickery[13] appears to warrant consideration. They believe the fault lies initially at the level of the thyroid cell and excess of thyroid stimulating hormone follows as a result of diminished thyroid hormone formation. Many of the above cited experimental findings are consistent with this theory. Even though Statland and his associates feel that the etiologic agent which initiates the epithelial degeneration in struma lymphomatosa is not of the same nature as the blocking agents (thiourea derivatives), Clausen's prolonged studies with thiouracil indicate that in some cases, after a long period of time, the thyroid epithelial cells apparently are not capable of undergoing hyperplasia but are atrophic and lymphocytic infiltrate occurs.

From our findings and from personal communications[19] with physicians in other parts of the lower Rio Grande Valley there appears to be an increased number of cases of struma lymphomatosa in the area. Since the lower valley is a definite geographic entity, we feel that there may be a factor in the environment which influences the formation of struma lymphomatosa. The area is a delta of the river and most of the water is derived from the mountains of northern Mexico around Monterrey with periodic floods from heavy

TABLE 2

CITY WATER ANALYSIS (RIO GRANDE RIVER)

Total solids	907 ppm
Total hardness	366 ppm
Calcium	107.2 ppm
Magnesium	21.8 ppm
Iron	1.54 ppm
Manganese	none
Sodium	5.2 ppm
Sulfate	211.6 ppm
Chloride	240 ppm
Residue on ignition	521 ppm
Fluoride	none
Iodide	.01 ppm

rains on the arid plains of northern Mexico and western Texas. Being near the sea it is not a region of endemic colloid goiter. Table 2 provides an analysis of the water supply in Brownsville.

The food of the area is influenced by Mexican customs and might possibly have a bearing.

What the similarity between our figures and those of Chesky, Dreese and Helwig and of Kisner indicates we do not know.

Summary

In 63 consecutive cases of thyroid disease, six or 9.5 per cent had struma lymphomatosa. We feel that there is a factor in the environment which may influence the formation of struma lymphomatosa. It may be an agent which influences the function of the thyroid cell.

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The Correlation Between the Uptake of I^{131}, Protein-Bound Iodine and Cholesterol Levels in Normal and Abnormal Thyroid States*

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UNTIL RECENT YEARS the only laboratory aids available in the diagnosis of thyroid disease were the determinations of the basal metabolic rate and blood cholesterol levels. Neither of these tests is a direct measurement of thyroid activity, and while the B.M.R. has been the time-honored test for thyroid function, its pitfalls and limitations are well known.[1-3] The reciprocal relationship between hyperthyroidism, hypothyroidism and blood cholesterol values has long been recognized, but cholesterol is subject to such great variation in apparently normal individuals, as well as many disease states, that its value as a diagnostic aid in thyroid disease is virtually worthless.[4,5] In 1933, Curtis, Davis and Phillips[6] demonstrated that the total iodine

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in blood was usually increased in hyperthyroidism and decreased in hypothyroidism. Technical difficulties made blood iodine determinations impractical in the average laboratory until Zak and associates[7] described the chloric acid method in 1952. A vast recent literature leaves no doubt that the PBI is a reliable test of thyroid activity. Most authorities accept 4 to 8 μg. per 100 ml. as the normal range but not all agree as to the point of beginning abnormality.[8]

A number of technics have been devised for measuring thyroid activity utilizing I^{131}.[9-11] The labeled iodine is absorbed from the gastrointestinal tract and is selectively concentrated by the thyroid follicle.[12] The gamma emissions of the radioactive I^{131} allow easy measurement of its concentration in the thyroid gland from any given dose in a given time. Utilizing a measuring instrument as sensitive as a scintillation counter allows administration of minute amounts (1.0 to 25 microcuries) of radioactive material. The total radiation effect has been calculated to be less than the patient would get from an x-ray examination of the gastrointestinal tract.[10] We accept values between 15 to 45 per cent as representing the normal range of uptake in euthyroid individuals, and values below 10 per cent and above 50 per cent as indicative of hypothyroidism and hyperthyroidism respectively.

Method

The individuals selected for this series were outpatients who had been referred to the laboratory for radioiodine (I^{131}) uptake studies. Prior to the administration of the tracer dose of I^{131}, blood was drawn with chemically clean

FIG. 1

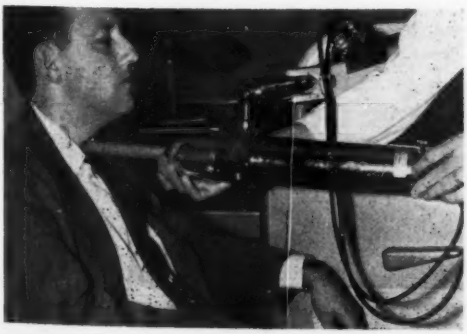


FIG. 2

syringes and emptied into two chemically clean test tubes. The serum from one tube was analyzed for total cholesterol content by the method of Bloor. The normal value for this method varies between 150 and 270 mg. per 100 ml. of blood. The second tube was used for protein-bound iodine (PBI) determination. The method used was the chloric acid digestion technic described by Leffler.[13] After the blood was drawn for the chemical tests, the patient was given a commercially available capsule, the inner surface of which was coated with approximately 25 microcuries of carrier-free NaI^{131}. Twenty-four hours later the patient returned to the laboratory and the uptake of I^{131} by the thyroid was measured with a scintillation counter (Fig. 1). The standard was simply another capsule of the same assay lot dissolved in warm water in a 50 ml. volumetric flask (Fig. 2). The capsules are delivered on demand by the manufacturer* and all capsules of a given lot are identical in potency within ± 2.5 per cent. This simplified method of receiving and distributing radioiodine (I^{131}) is relatively inexpensive, time and space-saving, and minimizes radiation hazards to personnel, and the possibility of contamination.[14] A history was obtained at the time of the uptake test and the patients were then classified as euthyroid, hypothyroid or hyperthyroid. The analysts of the PBI had no knowledge of the clinical evaluation or of the results of the I^{131} uptake.

Clinical Study

One hundred and sixty-four patients are in-

*Abbott Laboratories, Chicago, Ill.

TABLE 1

CONTROL SERIES

Case Number	I^{131}	PBI	Cholesterol	Clinical Appraisal
		$\frac{\mu g.}{100 ml.}$	$\frac{mg.}{100 ml.}$	
37	45%	5.6	247	Euthyroid
129	34	5.4	201	Euthyroid
139	30	8.1	208	Euthyroid 2 mos. pregnant
158	36	5.0	168	Euthyroid
164	43	5.5	242	Euthyroid
196	30	4.7	248	Euthyroid
238	36	4.2	231	Euthyroid
265	33	6.5	198	Euthyroid
285	30	2.7	183	Euthyroid
293	45	5.8	231	Euthyroid
309	38	6.0	216	Euthyroid
312	22	5.3	182	Euthyroid
330	33	5.1	264	Euthyroid
395	40	7.0	155	Euthyroid

cluded in this study, of which 115 were evaluated to be clinically euthyroid, four hyperthyroid and three hypothyroid. There were 27 males and 136 females tested. The youngest patient was 4 and the oldest was 71 years of age. The patients were referred by thirty-eight different physicians. Staff physicians, residents and technicians served as controls for this study. Table 1 shows the experimental values obtained on the control series of 14 cases with two exceptions, the values of uptake of radioiodine (I^{131}), protein-bound iodine (PBI) and cholesterol are within the normal range. The slight elevation of PBI noted in No. 139 should be considered a physiologic elevation

FIG. 3

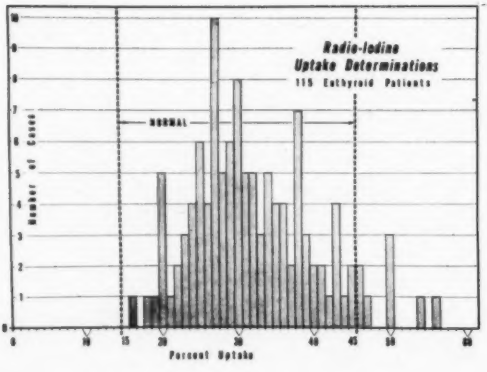
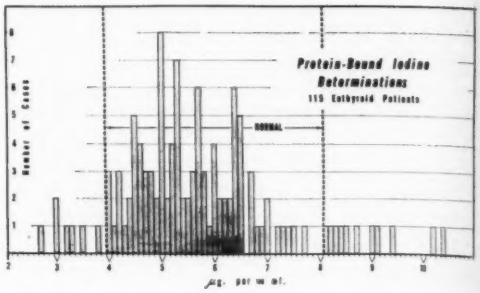


FIG. 4

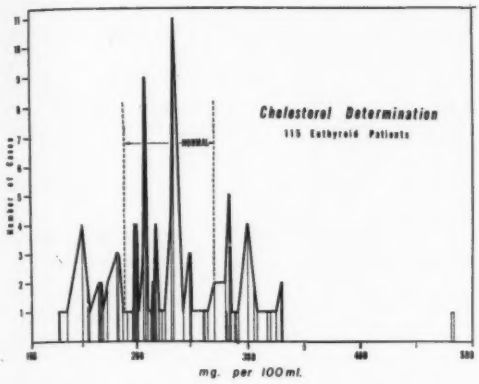


incidental to pregnancy.[15] It is important to point out that these test values represent single determinations. The euthyroid group includes our group of control patients and those who had nontoxic goiters and sundry complaints of nervousness, fatigue, weight gain, weight loss and the like. The lowest uptake (Fig. 3) of I^{131} in this group was 17 per cent and none of the uptake values was below 15 per cent. Eight (6.9 per cent) patients had uptake values above 45 per cent. If the upper limit of normal uptake of I^{131} is accepted as 50 per cent, then only two patients (1.7 per cent) fall outside of the accepted normal limits. From the standpoint of a diagnostic laboratory aid, the uptake of I^{131} by the thyroid appears to be a superbly accurate test.[2] The protein-bound iodine determinations are shown in figure 4 and it is noted that 18 values fall outside of our limits of 4 to 8 μg. per 100 ml., while 11 cases (9.5 per cent) had PBI values above 8.0 μg. per 100 ml. Of considerable interest is the fact that none of the high PBI values corresponded to the patients with elevated iodine uptake levels. An analysis of these facts seems to indicate that nearly 100 per cent of suspected euthyroid individuals can be so designated accurately if the diagnostic tests include both a PBI and a radioactive iodine uptake test. Figure 5 shows the cholesterol determinations in the same group of euthyroid patients. Only about 75 per cent of the values fall into the accepted limits of normal. We can only conclude that total cholesterol determinations are of little, if any, value as a laboratory aid in defining the euthyroid individual.

Hyperthyroidism

The frank case of thyrotoxicosis is usually

FIG. 5



sufficiently overt to make laboratory aids needless except for confirmatory purposes. This is not true in mild cases where the usual signs and symptoms are not well defined, and it is in this group of patients where laboratory aids are of vital diagnostic importance. Another group which will tax the clinical powers of the clinician includes patients with anxiety state, hypertension, chronic alcoholism and the like, and again laboratory aids are essential. Table 2 shows the tabulated results of uptake of I^{131}, PBI and cholesterol determinations in four cases of hyperthyroidism. There is a splendid correlation of the results of the uptake studies with the PBI, whereas the cholesterol values are low, only one case shows a true classical reciprocal relationship. The patients of cases 149 and 273 presented mild exophthalmos plus other typical features of hyperthyroidism. In case 429 there was mild diffuse enlargement of the thyroid gland, coarse tremor and a complaint of palpitation, fatigue, and a 15 pound weight loss in seven months despite a good appetite. Case 235 presented more of a diagnostic problem. This was a 46 year old man who complained of feeling "real shaky" and a weight loss of 25 pounds in two and a half months. There was no goiter nor other signs of thyroid disease. These results compare favorably with those reported in larger series.[2,16]

TABLE 2

PATIENTS WITH CLINICAL APPEARANCE OF HYPERTHYROID

Case Number	*I^{131}*	*PBI*	*Cholesterol*
149	81%	10.8	117
235	62%	14.0	166
273	55%	9.8	150
429	95%	16.0	181

Thyroiditis

We studied three patients with acute thyroiditis. The first case was that of a 34 year old white housewife. About four weeks before testing she had upper respiratory disease followed by enlargement and tenderness of the right lobe of the thyroid gland. She complained of lassitude and fatigue. Uptake studies showed a twentyfold diminution of activity over the involved lobe. After the uptake test she was treated with cortisone, the gland subsided and symptoms disappeared.

The second case was a 32 year old housewife whose youngest child was three and a half years of age. Ten days before, while vacationing, she noticed moderately severe pain in the anterior cervical region which lessened after about two days. About three days later the pain localized in the left lobe of the thyroid. When studied 10 days after the onset of her illness, the left lobe was visibly enlarged and was firm and tender to palpation.

The third case was that of a 17 year old white student nurse who was referred for testing because of slight enlargement of the left lobe of the thyroid, detected on routine physical examination. The left lobe was about one and a half times the size of the right lobe and was tender to palpation. There was a threefold diminution in activity with the radioiodine uptake test over the left lobe when compared with the right lobe.

In two of these cases there was striking diminution of radioactivity over the involved lobe and unfortunately the third case was not tested in this regard.

Werner[17] and associates reported on six cases of acute thyroiditis, all of whom had an abnormally low uptake of radioiodine. Keating and associates[18] noted similar findings in 16 patients. In the latter group he obtained PBI determinations in four cases and the values obtained were 4.4, 8.1, 9.3 and 9.6 μg. per 100 ml. These results compare favorably with ours. He also reported 7 cases of Hashimoto's thyroiditis, 5 of whom were myxedematous, with unequivocally normal uptake values.

TABLE 3

THYROIDITIS	Case Number	I^{131}	PBI	Cholesterol	Clinical Appraisal
Acute	402	2.5%	7.2 $\frac{\mu g.}{100 ml.}$	167 $\frac{mg.}{100 ml.}$	Euthyroid
	437	1.0	11.0	231	Euthyroid
	443	8.0	5.2	166	Euthyroid
Acute Thyroiditis Subsiding	444	20	2.6	210	
Chronic Hypothyroidism	1	1.3	1.2	366	Hypothyroidism due to chronic thyroiditis
	205	8.5	2.1	312	Hypothyroidism due to chronic thyroiditis
	221	1.0	1.0	283	Hypothyroidism post-partum 3 mos.

A fourth patient, No. 444, had thyroiditis four and a half months before testing and was treated with cortisone. After three months of treatment the swelling and tenderness subsided, but uptake of I^{131} by the involved lobe was one-third less active than over the opposite lobe. The uptake test was 20 per cent, the PBI was 2.6 and cholesterol was 210. We believe that we are justified in assuming that this represents a case of acute subsiding thyroiditis.

Two patients who were appraised to be clinically hypothyroid gave a history of thyroiditis in the past. The first was a 39 year old white housewife who had a swollen, tender thyroid gland 12 years before with a recurrence of the same symptoms three years later. Each bout of thyroiditis occurred approximately three months postpartum. Following the last bout of thyroiditis she was placed on thyroid therapy which was stopped six weeks prior to testing. When not taking thyroid she felt lethargic and gained weight. The second case was that of a 55 year old white housewife who had a bout of thyroiditis 25 years before. She had been taking thyroid for years and when the drug was stopped preparatory to testing, she complained of not feeling well and of weight gain. The results are summarized in table 3. It is our impression that the thyroid glands in these patients have undergone atrophy. The third case is that of a 29 year old colored woman, gravida III, para III. She was three and a half months postpartum when studied. She complained of extreme lethargy and was markedly obese with a recent weight gain and striking myxedema. After the initial uptake of 1 per cent was obtained she was given a dose of thyroid stimulating hormone (TSH) in the belief that this represented pituitary myxedema. The uptake test was then repeated but showed no appreciable change. There was a splendid correlation of data in these three cases.

Nodular Goiter

Ten patients were studied because of nodular goiters (Table 4). All cases were clinically euthyroid except No. 244, a 45 year old white housewife whose goiter appeared three years before. She was extremely nervous and complained of being "unable to relax." Radioactivity over the nodule was definitely greater than the activity of the opposite lobe. The first study showed a 47 per cent uptake of I^{131} (no PBI or cholesterol) and a second test six weeks later showed 35 per cent uptake

TABLE 4

NODULAR GOITER

Case Number	I^{131}	PBI	Cholesterol	Activity over Nodule
21	34%	4.8 $\frac{\mu g.}{100 ml.}$	190 $\frac{mg.}{100 ml.}$	↓
44	31	7.5	182	=
211	28	10.7	167	=
244*	47, 35	11.5	257	↑
299	20	4.6	291	=
303	19	3.2	148	↓
341	37	6.3	215	=
419	26	6.4	308	=
432	29	6.4	300	=
434	42	9.6	305	=

*Toxic nodule.

with 11.5 μg. per 100 ml. of PBI. Four months after surgical removal of the nodule she was clinically much improved and her uptake of I^{131} was 18 per cent. The PBI determination showed a distinct tendency to be elevated in this series of cases which may indicate that PBI is a better index of activity in nodular goiters than the uptake of radioiodine. One investigator[14] has noted an inverse relation between radioiodine uptake and the B.M.R. in a series of nodular goiters, and suggests that the intrinsic iodine want of nodular goiter may explain the variability of thyroid uptake of radioiodine.

Diffuse Goiter

Eight cases of colloid goiter were found in our series (Table 5). All of these patients were clinically euthyroid. Two patients had radioiodine (I^{131}) uptakes greater than 50 per cent and one showed an unexplained low PBI level. Cholesterol determinations were all normal except in one case where the value was 413 mg. per 100 ml. No single patient had more than one abnormal laboratory result. Others have recorded similar ranges of uptake values which probably reflect some moderate increased ability of the diffusely enlarged colloid-type goiter to accumulate iodine. The substernal goiter showed a PBI of 8.2 μg. per 100 ml.

Obesity or Weight Gain

Twenty-three patients were referred for study because of obesity, weight gain or difficulty in controlling their weight. The obvious implication in referring members of this

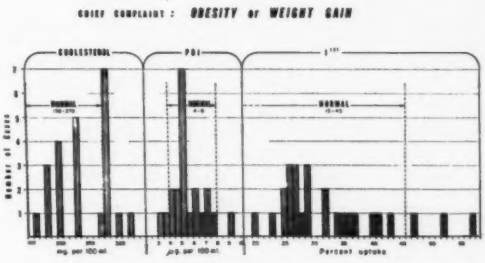
TABLE 5

DIFFUSE GOITER

Case Number	*I^{131}*	*PBI*	*Cholesterol*
		μg. / 100 ml.	mg. / 100 ml.
7	30%	1.7	200
13	30	6.8	216
282*	43	8.2	217
359	27	6.5	413
427	53	6.6	273
60	22	7.0	217
100	31	4.5	281
418	57	4.7	225

*Substernal

FIG. 6



group was to rule out hypothyroidism. In these cases we feel that this was conclusively accomplished (Fig. 6). The lowest radioiodine uptake value was 20 per cent and the lowest PBI was 3.0 μg. per 100 ml. Two uptake values exceeded 50 per cent but so many patients in this group have been on "reducing pills" of one sort or the other, many of which contained thyroid substance, that the slight increase in uptake of iodine may possibly represent a "rebound phenomenon"[16] which will be referred to later. One case showed the PBI elevated to 9.1 μg. per 100 ml. We can offer no explanation for this elevation. In nine of these cases there were high cholesterol levels. The laboratory data obtained from the radioiodine uptake and PBI generally supported our clinical evaluation of euthyroidism in this group, but cholesterol values seem to be of no diagnostic aid in this group.

Effect of Exogenous Thyroid Substance

Nine of our patients had been taking desiccated thyroid for varying periods of time. Reference to table 6 shows four patients with uptake values of radioiodine in the hyperthyroid group. Note that these patients had stopped taking exogenous thyroid from three to six weeks before the tests were performed while other patients who had stopped the drug the same period of time before testing had uptake values in the euthyroid range. Two patients were taking exogenous thyroid substance at the time they were tested and the uptake of radioiodine (I^{131}) in these cases was in the hypothyroid range. Greer[16] found essentially the same results in a group of 47 normal human subjects fed exogenous thyroid gland material. In one of his cases there was elevation of the radioiodine uptake tests eleven weeks after cessation of the hormone.

TABLE 6

NINE PATIENTS TAKING THYROID

Case No.	I^{131}	PBI	Cholesterol	Thyroid
			μg. / 100 ml.	mg. / 100 ml.	
436	57%	5.0	283	3 weeks ago
453	61	4.6	178	5 weeks ago
382	11	11.4	133	Still taking 2 gr./day
370	43	5.3	183	4 weeks ago
45	9	3.4	165	Now taking
	20	—	248	3 weeks ago
354	28	2.6	264	2 gr./day 2 weeks ago
263	50	5.0	266	5 weeks ago
232	27	7.4	233	6 weeks ago
452	62	4.2	150	4 gr./day—14 yr. 6 weeks ago

The usual subject gave euthyroid values two weeks after stopping exogenous thyroid, regardless of whether the patient had been taking the drug for a few days or for years. Greer explains the elevation of uptake following cessation of thyroid on the basis of a rebound phenomenon. Apparently there is a depression in pituitary TSH production due to exogenous thyroid and when the hormone is stopped, TSH production increases and the thyroid gland is thus overstimulated, and there is then a lag period until the endogenous thyroid secretion again inhibits the pituitary. The low PBI noted in one case may be explained on the same basis. Cholesterol values in this group were all normal.

Weight Loss

Twelve patients were studied because of weight loss. One had an iodine uptake of 50 per cent and two showed uptake values of 46 per cent. One patient whose uptake test was 28 per cent had a PBI of 10.4 μg. per 100 ml. The cholesterol values showed essentially the same variation that we have noted in other groups. These twelve patients were all evaluated as euthyroid individuals (Table 7).

Menstrual Irregularities

Thirteen cases were studied because of menstrual irregularities of one sort or the other. It has long been the practice of many gynecologists to treat these people with thyroid extract on an empiric basis. None of the 13 cases studied showed evidence of either hypo- or hyperthyroid disease but instead all fell in the euthyroid range (Table 8).

TABLE 7

WEIGHT LOSS

Case No.	Per Cent Uptake I^{131}	PBI	Cholesterol	Clinical Appraisal
52	16	6.4	266	Euthyroid
55	23	2.8	206	Euthyroid
67	32	4.0	206	Euthyroid
81*	50	6.7	300	Euthyroid
86	28	10.4	264	Euthyroid
140	32	5.3	150	Euthyroid
148	28	3.3	233	Euthyroid
210	37	6.4	183	Euthyroid
224	24	5.8	233	Euthyroid
348	46	6.1	206	Euthyroid
360	35	4.4	117	Euthyroid
425	46	4.5	289	Euthyroid

*On propylthiouracil eight years. Stopped eight months ago.

Conclusions

1. Uptake of radioiodine (I^{131}) and serum protein-bound iodine show splendid correlation in cases of frank hypothyroidism and hyperthyroidism.

2. It appears that in cases of acute thyroiditis there are low radioiodine uptake values, but cholesterol and PBI levels show no consistent variations. In our small series of cases of acute thyroiditis the uptake of I^{131} over the involved lobe was markedly diminished. One patient having subacute or resolving thyroiditis showed a normal uptake of I^{131} three months after the onset of the illness but at this time there was still diminished uptake of I^{131} over the involved lobe.

TABLE 8

MENSTRUAL IRREGULARITY OR INFERTILITY STUDIES

Case No.	Per Cent Uptake I^{131}	PBI	Cholesterol	Clinical Appraisal
23	23	5.2	270	Euthyroid
43	24	3.5	200	Euthyroid
451	41	4.9	127	Euthyroid
431	44	3.0	325	Euthyroid
435	38	6.0	305	Euthyroid
364	30	5.0	300	Euthyroid
350	50	3.2	198	Euthyroid
104*	14	3.9	182	Euthyroid
11	43	8.3	198	Euthyroid
442	56	5.4	220	Euthyroid
176	28	4.2	208	Euthyroid
14	31	5.0	233	Euthyroid
23	23	5.2	270	Euthyroid

*Took thyroid extract for 5 years.

3. We believe that the study of individuals for possible thyroid disease should include a radioiodine uptake study and a serum PBI determination. In our series certain cases showed either high or low values for one or the other test but in no instance was there a parallel change in both tests.

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Discussion (Abstract)

Question: We have two questions directed to Dr. Palmer. If he would like to come forward, the first one of these is, "What is the over-all precision of I^{131} alone in establishing thyroid functional status?"

Dr. Palmer. One of the slides I have shown indicates about a 98 per cent accuracy in evaluating the euthyroid individual with the radioiodine uptake test. This assumes that we accept the twilight zone of between 45 to 50 per cent as being within the normal range of iodine uptake. Of course, we will find some overlap of the euthyroid and hyperthyroid individuals in this range so that the clinical evaluation of the patient remains paramount.

The second question has to do with the uptake of I^{131} and PBI values after gallbladder studies. The iodine-containing contrast materials cause marked depression of the uptake values and will elevate the PBI. The contrast used for gallbladder visualization (Telepaque, Priodax and Teridax) will depress the uptake for about three weeks. Lipiodol and Pantopaque may be responsible for low uptake values for years after their instillation. The iodine containing materials used for intravenous urography are rapidly excreted and after about a week the patient should be a suitable candidate for an uptake test. Iodides are present in many cough syrups, and in the face of an unexplained low uptake result this facet should be explored.

Dr. Béla Halpert, Houston, Tex. The pathologist is in constant search to correlate structure with function. In the thyroid gland this can be accomplished quite accurately. If we think of the changes occurring in the thyroid gland produced by medication as phases in its function, it will help us to understand them. The unit structure of the gland is the acinus. This may be in one of three phases of function: in the resting phase, as Dr. Hazard pointed out, or in the secretory phase, or in the resorptive phase. Each of these phases has a definite morphologic appearance. For some years we have been giving in the diagnosis the phase of function of the gland, in the same way we state it in connection with reports on the endometrium. When the acini are in the resting phase they are lined by flat cells and their lumina contain a homogeneous pink colloid with no scallops and no vacuoles. When the acini are in the resorptive phase they are lined by tall columnar cells and their lumina are empty or contain a light stained colloid that is vacuolated and scalloped. When the acini are in the secretory phase they are lined by cuboidal cells and their lumina contain deeply stained homogeneous colloid with no vacuolization and no scallops. An understanding of these phases of function of the thyroid gland does not solve the problem but helps in the interpretation of the structural changes observed (Arch. Path. 41:155, 1946).

Dr. John L. Goforth, Dallas, Tex. It appears from the various discussions this morning, at least those I heard, that the poor old B.M.R. test is about to go by the board. I would like to ask Dr. Palmer if he would be good enough in a moment or two to evaluate the B.M.R. test in terms of present-day usefulness and in terms of his own experience.

Dr. Palmer (Closing). Well, Dr. Goforth, there are many cases where the B.M.R. is still a valuable method of testing for thyroid disease. It is of particular value in those patients who have been treated with radioiodine for thyroid disease and in whom the uptake studies are sometimes not practical. I think there was a recent article in the *J.A.M.A.* by Chinsky, who cor-

related the B.M.R. with the uptake test and found that there was a rather poor correlation. There are so many factors that will give abnormal B.M.R.'s, particularly in the group of patients who have cardiac disease or the group who are in an anxiety state, that the B.M.R. simply does not reveal the information we want. It seems to me that with the radioiodine uptake test, we are measuring a specific function, and the B.M.R., at best, is only an indirect test for thyroid disease.

A Resumē of Methodology in the Study of Thyroid Function*

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THE PURPOSE OF THIS PAPER is to summarize the present status of methodology designed to estimate the secretory activity of the thyroid gland. The types of estimation of thyroid function vary from relatively simple procedures, such as the determination of the metabolic rate, to complex estimations of the rates of thyroidal turnover and clearance which require the skill of a mathematical consultant to plot and estimate values. For the sake of brevity, this paper will concern itself with a consideration of the validity, technically, and the value, clinically, to the physician of those methods in most common use from the standpoint of economy to the patient, ease of manipulation and interpretation. These methods determine the basal metabolic rate, level of serum cholesterol, total protein-bound iodine (PBI) or serum precipitable iodine (SPI) and radioactive iodine uptake and release by the thyroid gland.

Basal Metabolic Rate

The basal metabolic rate is a measure of the rate of oxygen consumption by a subject under basal conditions which require that the subject be mentally and physically relaxed, awake and in a post-prandial state (12 hours). The rate of oxygen consumption can readily be computed in terms of calorie output. Many factors govern the rate of heat production under basal conditions—age, sex, glandular activity, muscular activity (smooth and skeletal), and the relative amounts of bone, muscle, fat and water in the organism, are among the more important. There is a progressive decrease in basal metabolic rate with advancing age,—most marked in the first two decades; females have about 5 per cent less calorie output than males of the same age. The rate of heat output is related to body surface. The measurement of body surface area introduces an error as great as 10 per cent.[1] Muscular tension and shivering increase the basal metabolic rate markedly without relation to the activity of the thyroid gland.

According to Werner[2] the B.M.R. has been found to correlate with the final clinical appraisal of thyroid activity in 50 to 80 per cent of patients. The 50 per cent figure predominates.[3-5] The sources of error have been detailed by Wilbrecht.[6]

There is an approximate error of 10 to 15 per cent because of instrumentation and the estimation of body surface. The technical demands are extended from personnel to include the patient. The personnel is too frequently not impressed with the importance of adequate preparation of the patient, as testing for leaks in the apparatus, comfortable fitting of the mask, loosening of clothing, and often is too disinterested to help the patient to relax emotionally. It is common to find the "second run" on the B.M.R. test very much smoother than the first. A wide variation in two estimations done a few minutes apart is attributable to "poor handling" of the patient or to poor cooperation on the part of the patient. Nervous tension induces

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irregular respiration and muscular tension. When these are combined with trembling the rate of oxygen consumption can rise to fantastic heights; obviously, conditions are no longer basal. Even with the best efforts it may be impossible to achieve success in a goodly number of patients even when ideal conditions for the test exist.

In addition, various conditions and diseases cause abnormal B.M.R. values even when there is no true disturbance of thyroid activity.[2] An increased B.M.R. may occur in cardiac or pulmonary decompensation and in severe anemia because of the increased work necessary to supply oxygen to the tissues. Pheochromocytoma increases the B.M.R. by virtue of secretion of epinephrine and decreased muscular relaxation. The increased values found in lymphomas are caused by the increased mass of metabolically active tissue. Low rates are encountered in wasting diseases and in panhypopituitarism. Children, asthmatics and elderly patients cooperate poorly.

With trained personnel and trained subjects one has the best chance of obtaining a fairly accurate result. Despite its handicaps the estimation of the basal metabolic rate will probably be retained as a standard routine procedure because of its value in detecting both hyperthyroidism and hypothyroidism. In addition, it is of value in patients who are excluded from other methods because of recent ingestion of iodine or thyroid-blocking drugs.

Serum Cholesterol

The concentration of cholesterol in normal human serum varies roughly between 110 and 320 mg. per 100 cc. Sperry[7] has pointed out that each normal person maintains a serum cholesterol characteristic for that individual even though the range of "normal" concentration may vary by 200 or more per cent. It follows that even doubling the serum cholesterol concentration of persons having a low serum cholesterol normally would give values within the so-called "normal" range. The lack of specificity of an elevated serum cholesterol is emphasized by rises in the serum level associated with disease in which there is no abnormality of thyroid function, for example diabetes, xanthomatosis, nephrosis, and obstructive jaundice; sharp decreases may be found in infectious diseases and pernicious anemia.

Peters and Man[8-10] have indicated that the disorder in hypothyroidism should not be termed hypercholesterolemia; it is properly a hyperlipemia with rather distinctive characteristics. Cholesterol is easier to measure than blood lipids and has been incorrectly used as an indicator of levels of blood lipid. The lipids of blood include free and esterified cholesterol and phospholipids. In normal individuals, despite variations in absolute level, the ratio of free to total cholesterol remains fairly constant (25 to 35 per cent) as does the ratio of free cholesterol to phospholipid. These normal relations are preserved in hypothyroidism. A hyperlipemia with disturbances of these ratios suggests that the disorder is not hypothyroidism or that there is a complicating disorder, e.g., hepatic disease. Neutral fat is present in small amounts in normal serum, and is not increased in uncomplicated hypothyroidism. A great increase in the level of neutral fat may be found in certain diseases (diabetes, nephrosis) with or without concomitant increase in cholesterol; the serum may actually be milky with a neutral fat content of 4 to 5 per cent. These considerations point to the conclusion that fractionation of lipids is more informative and less liable to misinterpretation than the simple estimation of plasma cholesterol.

The level of serum cholesterol, nevertheless, is usually elevated in hypothyroidism, and since we are primarily concerned with its diagnostic value some consideration of the mechanism of this elevation should be undertaken. In view of the similarity of the distribution of lipids in the serums of normal subjects and patients with hypothyroidism the suggestion is logical that the effect of the thyroid disorder is of a quantitative rather than a qualitative nature. Absence of thyroid function confers upon rats, dogs and humans the property of varying serum lipids in accordance with the diet. This effect can be abolished by giving thyroid extract. Rabbits fed cholesterol develop a high serum cholesterol even with an intact thyroid gland; in this respect the rabbit behaves uniquely like an athyrotic animal. Biosynthesis of cholesterol has been demonstrated using carbon 14 in acetate.[11,12] A low rate of synthesis occurs in animals fed cholesterol[13] thus protecting against an over abundance of cholesterol in the organism, and this might indicate that dietary cholesterol is not necessarily the etio-

logic factor in the aberrations of cholesterol metabolism that occurs in atherosclerosis. Evidence indicates that cholesterol is destroyed in the body[14] and excreted in the bile as cholic acid.[15]

Animal experiments indicate, in spite of their species difference, that thyroid hormone accelerates the synthesis of cholesterol and phospholipids in the liver and facilitates their destruction and excretion. Thyroid hormone controls the discharge of cholesterol and phospholipids from the liver to the blood since feeding cholesterol increases the concentration in the liver but not in the blood unless thyroid activity is impaired. The hyperlipemia of hypothyroidism apparently arises from impairment of destruction and excretion, and a lowering of the barrier of transfer from liver to blood. Although the cholesterol level regularly increases after total thyroidectomy and decreases when myxedema is corrected by administration of thyroid or thyroxin, the changes do not accurately reflect thyroid activity.[16] Serum cholesterol fails to rise in patients who on propylthiouracil medication develop hypothyroid stigmata; it is normal in patients with hypothyroidism secondary to hypopituitarism. The level of cholesterol in the blood in hyperthyroidism is worthless as a diagnostic aid.

From what has been said above, the disturbance of cholesterol level in hypothyroidism is relatively inconstant. The absolute level in the blood is not diagnostic ranging from 125 to 325 mg. per 100 cc. It embraces a very wide range of so-called levels. Even without associated disease the serum cholesterol is certainly not always elevated in hypothyroidism.[2] Elevation of the serum cholesterol is not diagnostic of hypothyroidism as it occurs in many other disorders. Complications in interpretation arise when hypothyroidism is associated with other disease which may raise or lower the level of cholesterol. It would appear that the disturbance of lipid metabolism in hypothyroidism is an exaggeration of the lipid metabolism of the individual with normal distribution of free cholesterol in relationship to total cholesterol and to phospholipids. Disturbance in these ratios would indicate that hypercholesterolemia may well be associated with some extrathyroidal disorder. Fractional serum lipid studies are more indicative of the true state than are serum cholesterol levels alone. The chemical methods, furthermore, carry an error of about 10 or more per cent. With modern and more accurate methods available today, less emphasis should be placed upon serum cholesterol levels and more on lipid metabolism disturbances or on other methods.

There is little evidence to support the assertions that hypercholesterolemia and low basal metabolism are reciprocal findings in hypothyroidism and that hypercholesterolemia in the absence of other causes is a better indicator of thyroid deficiency than a low basal metabolic rate. Nor can it be said that blood cholesterol levels may provide a guide in the treatment of thyroid disease, and that true thyroid deficiency is always accompanied by a hypercholesterolemia.[10] Exceptions to these cliches are too frequent to ignore.

Serum Precipitable Iodine

It is well established that whole blood contains both inorganic and organic iodine. The organic fraction is confined to the serum. The serum contains two fractions of iodine, one which precipitates with the proteins when they are separated by protein precipitants, and the other a fraction not precipitable by these reagents. The terms protein-bound iodine (PBI) and serum precipitable iodine (SPI) have been applied to the iodine fraction which is precipitated with proteins. The usual protein precipitant used is trichloracetic acid; the precipitate is washed free from inorganic iodine after which the iodine in the precipitate is measured by some analytic chemical procedure. It has been clearly established that the range of variation of serum precipitable iodine is fairly sharply demarcated in euthyroidism increasing in hyperthyroidism and decreasing in hypothyroidism.

The availability of SPI estimations marks the first instance in medical history in which the circulating level of a hormone can be measured directly; it is a very sensitive indicator of all levels of thyroid function. Its uses include value in diagnosis, measurement of response to therapy and even guidance in therapy. Its measurement makes possible the estimation of thyroid function in patients not suited to the determination of basal metabolic rate, e.g., in neurotics, children, patients with cardiac or pulmonary failure, and in instances where the metabolic rate is elevated or depressed without mediation of the thyroid gland.

The SPI of normal adults ranges from 4.0 to 8.0 μg. per 100 cc. with the mean closer to 5.0 than to 6.0 μg. The hypothyroid range is almost invariably lower than 4.0 μg. even less than 2.5 μg. per 100 cc.; 3.5 to 4.5 μg. may be borderline requiring clinical confirmation or a trial of treatment with thyroid substance. In hyperthyroid states the blood level of SPI lies between 12 and 16 μg. per 100 cc. of serum in frankly toxic cases. In these instances the estimation is hardly needed for diagnosis but may be of value in following the efficacy of treatment. The real value of the SPI in diagnosis lies in adding confirmation in suspected cases of borderline hyperthyroidism. A few hyperthyroid patients may have levels as low as 7.0 to 8.0 μg. per 100 cc. of serum. The extremes of range in hyperthyroidism are from 7.1 μg. to 30 or more μg. per 100 cc. of serum. Borderline cases may be tested by the clinical response to thyroid-blocking agents. Under ideal conditions of measurement, the accuracy of the method is about 90 per cent accurate in estimating the level of thyroid function.

The range of values for SPI is unaffected by race, sex and geography but physiologic changes can exert an effect. In pregnancy, the SPI rises to as high as 12 μg. per 100 cc. at about the middle of term,[17] and begins to decline twelve hours after delivery, returning to normal after a variable period of time.[18] The high levels in late pregnancy are unassociated with symptoms of hyperthyroidism. Pregnant patients with hyperthyroidism have higher levels than nonpregnant patients with equal toxicity.[19] Newborn babies approximate the mothers' blood levels ranging from 8 to 14 μg. per 100 cc.; by the end of four weeks the levels are within normal range and remain there in the absence of thyroid dysfunction until the fifth or sixth decade, at which time a slow progressive fall occurs in some cases although the level may be normal even in extreme old age.[20] Elevated values have been reported in acute thyroiditis and infectious hepatitis;[21,22] normal values are found in obstructive jaundice.

Low values of SPI are found in hypothyroidism, frank myxedema, nephrosis, cirrhosis and pituitary failure. The reasons for low SPI values in nephrosis and cirrhosis are not too clearly delineated. It is temporarily lowered following surgical trauma. Pituitary failure or insufficiency is associated with lowered SPI, though such patients do not show elevated serum cholesterol or myxedema in spite of great lowering of the basal metabolic rate. This may mean that extrathyroidal factors are involved in the lowered B.M.R. causing it to fall out of proportion to the coincident hypothyroidism occasioned by lack of thyrotropic hormone. If the administration of thyroid substance to normal individuals is stopped, the gland is inhibited for a time and low SPI values may be obtained.

The estimation of SPI is a difficult procedure technically, and is not available in the average hospital laboratory. Aside from personnel trained in exacting analytic technics, the quality of the reagents used and choice of method are important factors. Even when these are controlled one must be aware of drugs and medications which interfere to give false high or low values.

Iodides are frequent offenders, and as common ingredients of cough mixtures, vitamins and antibiotics (Neopenil), they adhere to proteins and are precipitated with the protein fraction. They give variable and unpredictable values for SPI. Their effect is dissipated some two or three weeks after the administration of iodide is stopped. Similar considerations apply to Lugol's solution and iodine containing amebacides. Ordinarily the butanol extractable iodine (BEI) effectively separates inorganic iodine from the thyroxine fraction. The BEI value is only 0.5 μg. per 100 cc. lower than the SPI and involves extra procedures. If iodides have been ingested, the extra trouble of estimating the BEI is compensated for, if immediate analysis is desirable. Unfortunately iodine compounds used in cholecystography, pyelography, bronchography and myelography not only raise the SPI but cannot be separated from thyroxine fractions by washing the butanol extract with alkali. These substances may interfere with accurate SPI determinations for weeks or months.

Desiccated thyroid will raise the SPI, depending upon the dose given; three or more weeks after medication has been stopped accurate levels may be obtained. Later, there may be a lowering of the SPI to hypothyroid levels because of inhibition of the thyroid gland. Mercurial diuretics may interfere with the determination by the formation of mercuric iodide which is not volatile,—this effect usually disappears twenty-four hours after

medication is stopped. Various thyroid blocking drugs, thiocyanate and thiouracil, lower the SPI for two or three weeks after their administration is discontinued; they exert their depressant action by blocking synthesis and secretion of thyroid hormone into the blood. Occasional high uptakes may occur due to the hyperplasia caused by the drug, persisting weeks after the drug is discontinued. The iodine of iodothiouracil will combine with protein and elevate the SPI variably; this iodine behaves like iodine in dyes used for radiography (vide supra). It has been reported[23] that unlike thyroxine, triiodothyronine may relieve myxedema and lower serum cholesterol without elevating the SPI above myxedema levels. If this is verified, it introduces a discouraging note when SPI is used to evaluate the clinical status in the course of triiodothyronine treatment.

In spite of the technical difficulties of estimation, and the limitations introduced by drugs and dyes, the SPI (or BEI) is probably the most accurate measure of the concentration of thyroid hormone in the circulating blood. It measures the functional status of the gland in hypothyroidism, euthyroidism and hyperthyroidism. This allows the clinician to follow the effects of therapy whether it be replacement, surgical, antithyroid drugs, or radioactive iodine.

Radioactive Iodine^{131} Technics

Chemical reactions are determined by the number of electrons in the outer shell of the atom, but isotopes differ in the structure of their nuclei; radioactive iodine^{131} behaves chemically and physiologically like stable iodine^{127}. Radioactive iodine is absorbed, stored, bound, synthesized into hormone and utilized like stable iodine. The radioactive isotope like "the glowworm's intricate movements during the summer night faithfully recorded by its phosphorescent light"[24] allows the intricate path of iodine in the body to be accurately identified. Under conditions of equilibrium, the rate of iodine uptake equals the rate of discharge from the gland; the rate of uptake thus allows one to estimate the rate of hormonal output from the untreated gland. A number of tests, designed to estimate the rate of uptake and release of radioactive iodine, are available to the clinician. These include the 24 hour radioiodine uptake test, the accumulation gradient, the thyroid clearance test, neck-thigh ratios, serum precipitable radioiodine (SPI^{131}), conversion ratios and certain ancillary technics. It should be noted that all radioactive iodine technics are interfered with by agents which block uptake of iodine, synthesis or secretion of hormone. In addition false high values occur in iodine-lack either dietary or post-surgical in origin.

The 24 hour radioiodine uptake test. In untreated patients, the uptake of radioiodine by the thyroid gland is probably a measure of the functional capacity of the epithelium in the gland. In this procedure, a tracer dose ranging from 10 to 100 μc. radioiodine is administered orally and the radioactivity over the thyroid gland is suitably measured 24 hours later. The ratio of counts over the gland to counts over a standard, with appropriate corrections for circulating radioiodine, is expressed as a percentage of the dose taken up by the gland. The value of this test depends upon the fact that the accumulation of I^{131} reaches a plateau in almost all levels of thyroid function within 24 hours. Some hypothyroid patients accumulate I^{131} well beyond 24 hours and some hyperthyroid patients have passed the peak and are discharging labeled hormone into the peripheral circulation; the error is not large. Radioautographs of the gland one hour after the injection of radioiodine show it to be protein-bound in cells within that time and uniformly distributed throughout the colloid in 24 hours.[25] Repeated uptake studies in the same individual may vary somewhat from time to time.

Different laboratories employ different standards of geometric measurement and so it is not easy to compare absolute uptakes of diagnostic percentage. For this reason a 35 to 55 per cent uptake[5,26-28] is regarded as the lower limit of hyperthyroidism in four different laboratories. Uniformity under standard conditions of measurement in a given laboratory is all that is needed for accuracy and diagnosis. In a series of 400 cases, embracing all levels of thyroid function, it was possible to achieve approximately 80 to 85 per cent accuracy in diagnosis.[29] Refinement of the procedure using adjunct methods, vide infra, may help considerably in more critical evaluation of patients in the twilight zone of overlap between euthyroidism and hyperthyroidism. The method is of less value in distinguishing hypothyroidism from euthyroid-

ism. The advantages of this method are many including economy both of time and expense, speed, which will allow ten to twenty estimations to be done in a morning in a well-equipped laboratory, accuracy of approximately 85 per cent in all levels of thyroid function, and applicability in all patients including those excluded from B.M.R. estimations,—neurotics, children, and cardiac and pulmonary invalids.

Limitations of the method include the overlap in the euthyroid and hyperthyroid range which may require differentiation by adequate clinical evaluation or testing by trial with triiodothyronine.[30] Since the method is primarily a measure of epithelial hyperplasia, levels of toxic uptakes may be found in goitrous myxedema.[31] One of the surprising findings is the poor correlation between per cent uptake and clinical toxicity. Toxicity apparently does not necessarily parallel the degree or quantity of epithelial hyperplasia. The greatest uptake occurs in the diffuse epithelial hyperplasia of Grave's disease, being less in toxic adenoma or nodular postoperative recurrence in spite of toxicity equal to Graves' disease. The method may fail significantly following I^{131} therapy for hyperthyroidism; in our series[29] 9 per cent of the patients showed uptakes in "the toxic range" some time after they were euthyroid clinically. Another limitation of the method is the interference of agents which block the uptake or turnover in the gland.

The 24 hour uptake of iodine^{131} lends itself to the diagnostic use of thyroid substance and triiodothyronine. This interesting test is based upon the fact that administration of thyroxine or desiccated thyroid to a euthyroid individual may depress or completely inhibit the 24 hour uptake of radioactive iodine.[32] The administration of thyroid in large doses does not depress the uptake of I^{131} by the hyperactive gland in toxic diffuse, or nodular goiter.[33] Since thyroid substance gives less clear results than L-thyroxine or crystalline L-triiodothyronine, Werner[30] has recently proposed a test using L-triiodothyronine because of its quicker action and shorter duration of effects after the drug is discontinued. Triiodothyronine is given daily by month in doses of 0.075 mg. for seven days. The 24 hour uptake of I^{131} is then done. A sharp drop in uptake to 20 per cent or less is indicative of euthyroidism; failure to find a significant drop is indicative of hyperthyroidism. This test greatly enhances the interpretation of 24 hour uptakes in "borderline zone" cases. The test has value as well in differentiating the euthyroid phase of Graves' disease with eye signs from the inactive phase of Graves' disease with eye signs; uptake in the former is not depressed whereas uptake in the latter is.

The thyroid clearance test. This test is a rather complex, time consuming, highly technical, and mathematical estimation which is primarily a research method at present. This clearance measures the volume of plasma cleared of I^{131} per hour. The value for thyroidal uptake is obtained by external counting over the thyroid gland, making proper correction for extra-thyroidal tissue effects. During the first few hours after the tracer dose is given, and before appreciable discharge has occurred from the gland, the slope of the uptake curve is a true measure of the rate at which radioiodine is increased in the gland. It is expressed as percentage of the dose given per hour. These data are compared with estimations of plasma radioactive iodine in percentage of dose per liter of serum. The plasma values are usually estimated at 45 and 75 minutes after an oral dose of tracer. The method is of no value in distinguishing hypothyroidism from euthyroidism because many euthyroid patients have an extremely low level of radio plasma. Euthyroid patients, by and large, will clear 0.5 to 3.5 liters per hour. The range in hyperthyroidism extends from 3.5 liters to 50 or more liters per hour. The rigidity of the technic alone mitigates against the method ever becoming popular as a routine clinical procedure. Refinements of the technic have recently been reported.[34-36] The method is of value in elucidating the physiology of the gland. Ingbar[35] has obtained significant data indicating that disturbed thyroid metabolism in Graves' disease is caused by increased thyroid mass, increased ability of unit mass to concentrate iodide, and an increased capacity of the gland to synthesize and elaborate hormone.

The neck-thigh ratio of Pochin[37] gives results almost as accurate as the thyroid clearance rate and is far simpler to perform. Under controlled conditions of arrangement of the counter, geometry, and background counting,

the ratio of counts over the neck to those over the thigh two hours after a tracer dose (7 μc.) is determined. A neck-thigh ratio of 7.0 is regarded as the upper limit of normal for euthyroid patients, being exceeded in only 4 per cent of subjects without known thyroid disease. The coefficient of correlation in a group of 54 patients with and without hyperthyroidism was 0.94. This test is accurate, simple and can be completed in two hours.

Serum precipitable radioiodine (SPI^{131}). The estimation of SPI^{131} measures the rate of release of thyroid hormone from the gland. Studies indicate that in toxic cases tagged hormone may be found in the circulation within two to eight hours after administration of the isotope; at the end of 24 hours as much as 75 per cent of the radioactivity of the serum may be in the organic fraction in hyperthyroidism; about 20 per cent of the radioactivity in the serum of euthyroid patients is in the organic fraction at the end of this time. Measurements may be done at the end of 48 and 72 hours because the 24 hour measurement is complicated by high values for circulating inorganic SPI^{131}. The measurement of SPI^{131} has only slightly higher diagnostic accuracy than the measurement of SPI,[38] offering about 90 per cent correlation with the final evaluation of thyroid function in distinguishing hyperthyroidism from euthyroidism. The results are of no value in hypothyroidism. The overlap between euthyroid and hyperthyroid data is greater at 48 than at 72 hours and the latter is the preferred time for the estimation. The values in euthyroidism extend up to 0.3 per cent of the administered dose (50 to 100 μc.); 0.3 per cent or more is in the hyperthyroid range. If more than 0.3 per cent is found it is best to confirm the result by measuring the radioactivity of the protein precipitate. The main advantage of SPI^{131} determinations over SPI determinations is that they avoid the elaborate chemical technics necessary to estimate SPI, the SPI^{131} estimation being somewhat more accurate. Its chief disadvantages are the 72 hour delay in getting a report and the abnormal effects of thyroid-blocking dyes and drugs.

Conversion ratio. The ratio of SPI^{131} to total plasma I^{131} (which includes both organic and inorganic I^{131}) 24 hours after a tracer dose (50 to 200 μc.) is administered, expressed as percentage is the conversion ratio. This ratio is of value in differentiating hyperthyroidism from euthyroidism. Many presumed euthyroid patients have such low conversion ratios that the method does not distinguish euthyroidism from hypothyroidism. Seed and co-workers[38] and Sheline and Clark[39] found the conversion ratio to be more accurate than any other routine test with radioactive isotope. They compared the conversion ratio for accuracy with 24 hour I^{131} uptake, 24 hour I^{131} urinary excretion and total plasma I^{131}. A sharp separation between euthyroidism and hyperthyroidism occurs at 35 per cent (4 per cent of hyperthyroid patients fall below this level and only 2.4 per cent above it).

Urinary excretion methods. These were among the early popular tests that have numerous objections to their use. They purport to measure the iodine rejected by the thyroid gland. Their validity may be seriously questioned[40] because of poor correlation between the radioiodine count over the gland and the total iodine excretion, even when the gland is totally removed surgically.[41] Further disadvantages are the wide overlapping of values in hypothyroid, euthyroid and hyperthyroid patients. Accurate collections of urine are virtually unattainable, especially in females, without the facilities of a metabolic ward. Significant errors occur in cardiac and renal disease. A high renal excretion (associated with low thyroidal uptake) and a high B.M.R. indicate extrathyroidal hypermetabolism; such instances are found in pheochromocytoma, Parkinson's disease, alcoholism, thyrotoxicosis artifacta.

Ancillary radioiodine tests. These adjunct methods include topographical survey, autoradiography and radiochromatography. In topographical survey by directional Geiger-Muller or scintillation counters, the tracer dose, picked up by functioning thyroid tissue, can aid materially in the diagnosis of a variety of clinical conditions including impalpable thyroid masses, retrosternal thyroid prolongations, juxtathyroid ectopic rests, pelvic ovarian rests, well-differentiated metastatic malignancy and encroachments on the gland, benign and malignant. The scintillation gammagraph of Allen and his co-workers[31] "photographs" radioactive tissue to give information as to size and shape of functional and nonfunctional tissue. After a 200 μc. tracer dose, before thyroidectomy, slices of gland removed at operation have enough radioactivity to

darken a photographic plate, the darker areas corresponding to areas of increased radioiodine uptake. Radiochromatography combines the use of radioiodine with paper chromatography. Its use is new and holds great promise. By using the solvent butanol-acetic acid in one dimension and butanol-dioxan ammonia in the second, Gross and Pitt-Rivers[42] identified the second thyroid hormone triiodothyronine. Clinical laboratory methods for the estimation of protein-bound iodine are available albeit at considerable expense in equipment.

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Discussion (Abstract)

Dr. P. C. Johnson, Oklahoma City, Okla. I have been involved with radioactive iodine therapy in two university medical centers. In each the dosage of radioactive iodine is determined by an "educated" guess by the clinicians concerned. In each instance the percentage of cures after one treatment dose and the percentage of failures closely approximates the figures presented today. One wonders if it is worthwhile to purchase a $2,000 machine, require several days of pretreatment "work-ups," and use an empirical formula which fails to take into account irregularities of the surface and thickness of the gland. Since this presentation fails to give the range of doses used, one is unable to see whether the therapeutic dose range is expanded or contracted by this technic.

Secondly, I have observed that a median dosage of 11 millicuries is required for treatment in Michigan while in Oklahoma a median of 8 millicuries seems adequate to obtain the same result. Could this mean that the thyroids of the people in Oklahoma are different from those in Michigan, or does this mean that thyroid response is not closely correlated to small changes in dosage?

Subtotal Ablation of the Thyroid Gland with a Single Dose of Radioactive Iodine-131 for the Treatment of Thyrotoxicosis*

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Introduction

THE PURPOSE OF THIS PAPER is to report on the results of a four-year follow-up study of 142 cases of thyrotoxicosis treated with a single dose of radioactive I^{131}. This is not a report on the response to multiple doses or fractionated doses of radioactive I^{131} used for the treatment of thyrotoxicosis. In this investigation, inability to relieve all signs and symptoms of the disease or to produce a "cure" with a single dose has been considered a failure. In this respect this method of radioiodine therapy can be considered as similar to the surgical method of approach in the treatment of thyrotoxicosis. From our studies it has been found that 7,000 reps. to the thyroid gland administered as a single dose removed approximately one-half of the functioning thyroid gland, resulting in a change from the hyperthyroid to the euthyroid state in 87 per cent of the patients treated. It has been our premise that a single dose of radioactive I^{131} should produce a cure just as a thyroidectomy should produce a cure, if this method is to be more widely accepted. It is our opinion that this is an ideal method of approach for many reasons, since multiple administrations of radioactivity represent an increased and unnecessary hazard to the patient. Although this paper is concerned with only four years of experience with this single dose method, the study was begun six years ago, in 1949. At that time a program for the evaluation of I^{131} therapy in thyrotoxicosis was established in which: (a) the radiation dosage to the thyroid gland would be calculated by the method suggested by Marinelli and Quimby;[1,2] (b) the weight of the thyroid gland would be calculated by an empirical formula by Allen,[3] rather than *estimated* by the clinician based upon an "educated guess" using the fingers as calipers; and (c) the maximum pretherapy thyroid uptake of the orally administered radioactive I^{131} and the pretherapy effective half-life studies would be determined by the conventional methods of detection, using a wide-angle scintillation counter.

How does the single-dose method differ from multiple-dose technics?

In the multiple dose technic the oral dose of I^{131} is given and, if symptoms and signs are not completely relieved within a period of two to eight months, a second dose of I^{131} is administered. If this fails to produce a cure, additional doses are given until the desired therapeutic response is obtained. Eventually, almost all of the patients are relieved of their signs and symptoms. The oral dose, when this method is employed, is usually based on different criteria, varying from clinic to clinic. Generally speaking, the *estimated size* of the gland, the elevation of the B.M.R., and the degree of clinical toxicity are a few of the factors influencing the amount to be administered. In a review of the literature, when the multiple-dose method is employed, generally no attempt is made to determine the effective half-life and/or the weight of the thyroid gland, and if the thyroid weight is considered it is estimated by palpation and inspection. The multiple-dose method has certain disadvantages, the principal one being that treatment is unnecessarily prolonged. Patients

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treated by this method have commented that were they to need treatment again they would choose or select a method which would produce a more rapid cure. In addition, with the multiple-dose procedure, larger oral doses of radiation are required to produce the same end effect, resulting in unnecessary exposure of extrathyroidal tissues and organs to ionizing radiation.

How does this method differ from the single-dose method advocated by other clinics?

In the single-dose method employed in our clinics, the weight of the thyroid gland is not estimated but is *calculated* from the thyroid silhouette called the thyroid gammagram which is obtained by an automatic device which scans the radioactive gamma-emitting thyroid gland.[4] This is essentially the only difference between the technic published by other authors using a single-dose method in which the Marinelli-Quimby formula for the determination of tissue dosage has been used. An empirical formula for thyroid weight determination was developed[3] based on thyroid glands removed at necropsy, which showed that the mean depth or thickness of each thyroid lobe was approximately one-third of the height of the lobe. From this and the surface area of each lobe which is obtained from the thyroid gammagram, volume and weight of the thyroid gland can then be mathematically calculated with an accuracy of ± 10 per cent.

Selection of Cases for Therapy

A total of 142 cases were studied in this investigation. For the purpose of the investigation, 107 (75.4 per cent) of these were included in the analysis of therapeutic results; 35 cases (24.6 per cent) were discarded, two cases because of vomiting the orally administered dose shortly after administration, and 33 cases because insufficient time had elapsed for adequate follow-up and which included only those patients followed for less than four months. The majority of patients included were private patients referred by the clinicians in the community to the Radioisotope Department of The Methodist Hospital. Also included in this series were charity cases referred by The Methodist Hospital, The Jefferson Davis Hospital, and St. Joseph's Hospital, all in Houston, Texas. Thirty-two (22 per cent) were veterans treated at the V.A. Hospital in Houston. The same pretherapy, therapy, and post-therapy protocol was followed in the treatment of each patient from each hospital. All patients had the same pretherapy preparation and the eight to ten day pretherapeutic diagnostic "work-up" including a thyroid uptake, thyroid gammagram, and effective half-life determined over five consecutive days. A complete history and physical examination were done according to the prearranged protocol designed especially for this investigation. In addition, laboratory studies such as serum cholesterol, B.M.R., and serum protein-bound iodine were done.

Classification of Cases

Vital Statistics. Of the 142 patients treated over the past four years, 116 (81.7 per cent) were Caucasian, 18 (12.7 per cent) were Negro, 6 (4.2 per cent) were Latin-American, and 2 (1.4 per cent) were Oriental. Eighty-five (59.9 per cent) were female and 57 (40.1 per cent) were male. The higher incidence of thyrotoxicosis occurring in the males in this series is probably due to the fact that one of the hospitals (V.A. Hospital) included in this investigation involved predominantly a male population. The number of females treated, exclusive of the veteran population, was 84 (76.4 per cent of all nonveteran cases) which is more nearly the ratio of approximately 4 to 1 which is generally accepted. Of the 142 cases, 70 (49.3 per cent) females were Caucasian, 9 (6.3 per cent) were Negro, 5 (3.5 per cent) were Latin-American, and one (0.7 per cent) was Oriental. Of the 85 females, 80 (94.1 per cent) were married and 5 (5.9 per cent) were single. Of the 142 cases, 46 (32.4 per cent) males were Caucasian, 9 (6.3 per cent) were Negro, one (0.7 per cent) was Latin-American, and one (0.7 per cent) was Oriental. It is of interest to note that 126 (88.7 per cent) of the males and females with thyrotoxicosis were married and only 11 (7.7 per cent) were single. The mean age of the 142 patients of thyrotoxicosis was 41.6 years, the ages ranging from 12 to 70 years.

History of Previous Therapy. Of the 142 cases treated, 67 (47.2 per cent) had no previous antithyroid therapy or thyroid surgery; 47 (33 per cent) had a history of recent or remote antithyroid therapy prior to I^{131} therapy; 30 had received recent antithyroid therapy

(within two months preceding radioiodine therapy); and 18 had received remote antithyroid therapy (two months or more before radioiodine therapy). Of the 142 cases treated, 25 (17.6 per cent) had previous thyroid surgery on one or more occasions. Three cases (2.6 per cent) were treated with radioactive iodine concurrently with therapeutic doses of antithyroid compounds in an effort to determine whether or not it was necessary to discontinue antithyroid therapy in the very severe cases of thyrotoxicosis. The pretherapy I^{131} studies, the therapeutic procedure, and the postherapy follow-up were done while the patient was concurrently receiving either propylthiouracil or Tapazole. One hundred and seventeen (82.4 per cent) of the cases treated had no previous thyroid surgery. The 10 patients having previous thyroid surgery but no previous antithyroid therapy, either recent, remote or concomitant, are shown in table 1.

Anatomic and Physiologic Findings. Of the 142 cases treated, 25 patients (17 per cent) had previous surgery and, for the purpose of this investigation, no attempt has been made to classify the residual postoperative thyroid tissue into a nodular or diffuse category. Of the 117 (82.4 per cent) remaining cases in which there had been no previous thyroid surgery, 109 (93.2 per cent) had diffusely enlarged thyroid glands with no evidence of hypofunctioning or hyperfunctioning nodules determined either by palpation or from the thyroid gammagram. There were eight (6.8 per cent) instances of nodular toxic goiter. Of the nodular glands treated, none had hyperplastic nodules and all contained hypofunctioning nodules, the toxicity being produced by the hyperplastic perinodular non-nodular tissue.

Clinical Data (Signs and Symptoms). Prior to radioiodine therapy, all cases were examined according to a predetermined protocol and the severity of the disease was determined

TABLE 1

CLASSIFICATION OF 25 CASES OF THYROTOXICOSIS HAVING PREVIOUS THYROID SURGERY

	Number	*Per Cent*
No previous antithyroid therapy	10	40
Recent antithyroid therapy	7	28
Remote antithyroid therapy	6	24
I^{131} therapy while on antithyroid therapy	2	08
	25	17.6

TABLE 2

PRE-I^{131} THERAPY EVALUATION ON 142 CASES OF THYROTOXICOSIS ACCORDING TO SEVERITY

	Degree	*Number*	*Per Cent*
	1+	7	5.7
	2+	50	40.7
	3+	65	52.8
	4+	1	0.8
Severity graded		123	86.6
Severity not graded		19	13.4

before therapy and after the history and physical examination were done and the protocol completed. A careful scrutiny of medications containing iodides or diagnostic procedures containing iodides was made in every case. Nineteen (13.4 per cent) of the 142 cases treated failed to have a record of the severity of the disease recorded as determined by the examining physician. One hundred and twenty-three (86.6 per cent) were graded according to severity in accordance with the protocol, the degree of severity ranging from 1 + to 4 + (Table 2).

Of the cases treated 93.5 per cent were graded as either 2 + or 3 + in severity. All of the final grading was done by the same physician who saw the patients before and after treatment. Two of the most significant objective signs that have been most helpful in evaluating response to radioiodine therapy have been body weight and radial pulse. The mean pretherapy radial pulse rate of those patients having no previous surgery was 103 per minute. The 25 cases which had thyroid surgery previous to radioiodine therapy had a mean radial pulse of 100 per minute. The mean pretherapy radial pulse of 102.5 per minute was recorded for all cases studied.

Laboratory Data. The principal laboratory tests used in this investigation for the evaluation of the results of radioiodine therapy were the serum cholesterol, B.M.R., and serum protein-bound iodine determination. Of all cases treated, 35.9 per cent had at least one pretherapy PBI determination; 54.9 per cent of all cases had at least one pretherapy B.M.R.; and 64.1 per cent of all patients treated had at least one pretherapy serum cholesterol determination. Table 3 shows the mean values for the PBI, B.M.R., and serum cholesterol before treatment.

Pretherapy tracer *thyroid uptake studies* were repeated one to three times before treat-

TABLE 3

PRE-I^{131} THERAPY EVALUATION OF 142 CASES OF THYROTOXICOSIS ACCORDING TO LABORATORY DATA

	*P.B.I.** μgm. per 100 cc.	*B.M.R.** per cent	*Cholesterol** mg. per 100 cc.
No previous history thyroid surgery	12.9	+35.5	181
Previous surgery for thyrotoxicosis	9.4	+27.3	212
All cases	12.5	+34	186

*Mean values

ment. The mean values and ranges are shown in tables 4 and 5.

Indications and Contraindications for Treatment

It has not been felt that the age limitation of 40 to 45 years imposed in some clinics throughout this country is a justifiable one. In our series, all adult cases of thyrotoxicosis were considered as candidates for radioiodine treatment, with certain exceptions. The rationale for imposing an age limitation has been principally because of the possible carcinogenic effect of I^{131}. It was felt that this was something which only time can tell and that the answer must be deferred for the present time although the consensus is that this possibility is very remote. It is of interest that the thiouracil drugs have also been accused of being carcinogenic. The work of Goldberg and Chaikoff,[5] who have produced thyroid cancer in rats, using amounts of I^{131} of at least twenty times larger than that used in the treatment of thyrotoxicosis, is not to be ignored. It is questionable, however, whether this evidence can be applied to the human patient. The amount of I^{131} used by Goldberg and Chaikoff in rats is of the magnitude used in human beings in the treatment of cancer of the thyroid. The recent work reported by Clark[6] and Uhlmann[7] of the possible relationship between irradiation by x-ray and thyroid cancer in 13 children and adolescents is of interest. It has not been felt, however, that this observation alone is adequate justification to eliminate I^{131} therapy as a modality in the treatment of juvenile thyrotoxicosis. A comparison of the post-therapy signs and symptoms in adult thyrotoxic patients who have been made euthyroid with antithyroid compounds, with the signs and symptoms of the same patients who were later treated with radioactive iodine has consistently shown that patients feel better and do better following the radioiodine therapy than when taking the antithyroid compound. The youngest patient of our series was 12 years of age. Antithyroid compounds have been used in our clinics in juvenile thyrotoxicosis if the thyroid gland is normal or near-normal in size. If the clinical picture and laboratory data indicate thyrotoxicosis and the thyroid gammagram shows the gland to be at least 50 per cent larger than normal, it is felt that the enlargement is indicative of a chronic process and the process is not likely to be reversed with antithyroid therapy. Maloof[8] has recently shown that the cellular hypertrophy and nuclear changes that are seen following the radiation of the thyroid gland in rats following exposure to ionizing radiation of I^{131}, which have in the past been attributed to the primary effects of ionizing radiation, are probably secondary to thyrotropic hormone stimulation by the pituitary, since such changes can be partially inhibited by hypophysectomy or by the administration of DL-thyroxine. Similar morphologic changes have also been demonstrated in the thyroid gland of human beings following radioiodine therapy for thyrotoxicosis.

All patients referred with diffuse toxic goiter, whether primary, or persistent or recurrent following antithyroid therapy or thyroidectomy, were considered candidates for radioiodine therapy, including exophthalmic goiter. There has been no evidence of any significant progression of exophthalmos in those patients treated with I^{131}.

Exophthalmic readings with the Bahn D.B.P. exophthalmometer were made prior to radioiodine therapy and at each follow-up visit following therapy, by the same individual. Increase of one or two millimeters was frequently noted. It was felt that this increase was paradoxical due to a technical artifact brought about by the reduction in the periorbital edema, particularly of the tissues overlying the bony prominence in the region of the external canthi.

Patients with nodular toxic goiter in whom the nodules were hypofunctioning or nonfunctioning, as demonstrated by the thyroid gammagram, and in whom the toxicity was due to the perinodular tissue, were also considered candidates for radioiodine therapy;

however, only a few were accepted for treatment. Radioactive I^{131} in this type of goiter is as effective as in a diffuse goiter and results in the ablation of the hyperplastic perinodular tissue responsible for the toxicity. However, the nonfunctioning or hypofunctioning nodules are generally unaffected. When it is felt that a "hobnailed" thyroid would result which would be objectionable for cosmetic or obstructive reasons by virtue of the location of the nodules, such cases are not considered ideal candidates for radioiodine therapy. For these reasons the majority of the nodular toxic goiters seen in our clinics have been referred for surgery.

We have had very little experience where the toxicity was due to solitary or multiple hyperplastic nodules. In seven years' experience with over 500 thyroid gammagrams, only one or two proven cases have been seen in which the toxicity was felt to be due to a nodule or nodules. Because of our inexperience in this field, we have felt that all such patients should be treated surgically. Although it is not the subject of this paper, it might be said at this time that patients having solitary or multiple hyperplastic *nontoxic* nodules, which in our experience are as rare as their toxic counterpart, are likewise referred for operation and have not been considered candidates for radioiodine therapy. Other contraindications to radioiodine therapy have been pregnancy in *any* trimester, or during the postpartum period if breast feeding is indicated or cannot be discontinued. Juvenile thyrotoxicosis is a contraindication if the process is acute and of short duration and there is no demonstrable enlargement of the thyroid gland greater than 50 per cent as determined by the thyroid gammagram.

Technic

Our method of thyroid uptake is essentially the same as that practiced by other clinics, with the exception that a "close-up" technic[9] of detection is used. This enables us to use small tracer doses of one microcurie of I^{131} orally. For the past 18 months our thyroid uptakes, as well as all other types of diagnostic procedures done in our clinics, have been done with sodium iodine gamma-ray spectrometry technics, using pulse-height analysis.[10] Prior to this we used the conventional scintillation sodium iodide or calcium tungstate detectors used in conjunction with an integral bias system. The majority of the studies, however, were done with this latter method.

The pretherapy preparation of the patient requires between eight and ten days. There is no necessity for hospitalization unless the severity of the thyrotoxicosis warrants hospitalization. The majority of the patients included in this series were treated on an outpatient basis. The three diagnostic criteria required for the determination of the oral dose of radioactive I^{131} to be administered are determined during this pretherapeutic diagnostic period and are; (a) the thyroid uptake, (b) the effective half-life, and (c) the weight of the thyroid gland. The *first diagnostic criterion* necessary to determine the oral dose is the *thyroid uptake*. One microcurie of carrier-free radioactive I^{131} in 20 cc. of water containing a green food coloring material is administered orally to the fasting patient. The container is an Armstrong-labeled-Rite capsule vial, 8-dram size, manufactured by the Armstrong Cork Company. The individual doses are all prepared in our laboratory and are not purchased commercially. They are prepared weekly in advance of the intended use and each individual dose is counted immediately prior to administration to the patient. The bottle is rinsed three times with water and these washings are drunk through a cellophane straw by the patient. Routinely the patient returns for a 3 hour, 6 hour, and 24 hour thyroid uptake determination. No effort is made to collect the patient's urine. For the actual thyroid uptake study, the patient is placed in the recumbent position with the anterior surface of the neck horizontal. The scintillation detector tube is centered over the isthmus, if palpable, otherwise the tube is centered 5 cm. below the notch of the thyroid cartilage. The end of the scintillation detector tube is placed 2.6 cm. from the skin of the neck. The background activity of the extrathyroidal neck structures are determined by *counting* and subtracting the activity present in the leg just above the knee from the gross activity found over the thyroid region.

The *second diagnostic criterion* required to determine the oral dose is the *effective half-life* of the isotope in the thyroid gland. The patient returns twice daily for 3 to 5 consecu-

tive days for these studies. The patient is placed in the recumbent position beneath the detector tube exactly as for the thyroid uptake, and the radioactivity remaining in the thyroid gland from day to day is determined. This gives the information necessary to determine how long the radioactive iodine concentrated by the gland will remain in the gland of each individual patient, since the rate of release of radioactivity is known to vary from patient to patient. This information is then plotted on semilog graph paper and the E.H.L. determined. Following the effective half-life studies, further thyroid uptake studies are done, if necessary, or if the patient is in the hospital, in order to detect any change in thyroid function brought about by bed-rest.

The *third* and a *very important diagnostic criterion* is the *thyroid weight*. To arrive at this, it is necessary to "estimate" the weight of the thyroid gland so that an oral dose of I^{131} can be given to the patient that will result in a concentration of 4 to 6 microcuries of I^{131} per gram of thyroid tissue. This is analagous to the need of adequate visible light for the production of a good photograph. In this case we are dealing with invisible light or photons (gamma rays), and to obtain a good thyroid "picture" or thyroid gammagram there must be adequate "light" or gamma rays being emitted by the radioactive iodine concentrated in the thyroid gland. In our experience 4 to 6 microcuries of I^{131} per gram of estimated thyroid tissue are sufficient to produce a satisfactory thyroid gammagram if sodium iodide gamma-ray spectrometry is used in connection with a single-channel pulse-height analyzer. For the conventional sodium iodide (1 in. by 1 in. by 1 in.) or calcium tungstate (¼ in. by ¼ in. by 1 in.) columnated detectors using a ¼ in. aperture, 2 to 4 microcuries of I^{131} per gram of estimated thyroid tissue were found sufficient.

After the thyroid weight has been estimated, the oral dose of I^{131} that will give 4 to 6 microcuries per gram of estimated thyroid tissue can be calculated from the formula:

$$\frac{\text{estimated weight of gland} \times \text{4-6 microcuries}}{\text{maximum \% thyroid uptake}} = \text{oral gammagraphic dose } I^{131}$$

Twenty-four hours after the administration of the gammagraphic dose of radioactive I^{131}, the patient returns and an anteroposterior gammagram of the thyroid gland is done. The time required for this test is approximately 15 to 30 minutes, depending on the area to be scanned. The patient is placed in a recumbent position with the head and neck hyperextended so that the anterior surface of the neck is horizontal. The head is immobilized with a Flexicast rubber bag containing plastic beads of uniform size and connected to a vacuum system. Complete cooperation of the patient is essential since the same standards necessary for good photography also apply here. Frequently sedation is given to allay the anxiety of the hyperthyroid patient and minimize the movement of the patient's body, especially of the arms and legs. Demerol, 50 to 100 mg. intramuscularly with or without Thorazine 25 mg., is usually sufficient. Occasionally Seconal, Gm. 0.1 will suffice. Any movement of any part of the patient is discouraged and the patient is instructed to swallow only when the scanning tube is far to the patient's right or left and off the patient's neck. The distal end of the detector tube is kept in contact with the patient's skin in order to prevent unnecessary "distortion" of the thyroid gland. Because of the irregular contour of the neck of patients, frequent adjustment of the tube during the scanning procedure is necessary.

The thyroid gammagram is a "photograph" of the thyroid gland made from invisible light (gamma rays) emitted by the radioactive iodine that is trapped in and bound by the thyroid gland during the synthesis of thyroid hormone. The thyroid gammagram gives the distribution of radioactive iodine within the substance of the gland, and from this initial pattern of distribution not only can the size, shape, outline and location of the thyroid gland be determined, but also the presence or absence and the physiologic function of nodules can be determined. This latter observation is an interesting one but will not be discussed at this time and is a subject for subsequent publication. From the silhouette of the thyroid gland, the perimeter of each lobe can be drawn. Where to draw the line representing the perimeter of the gland is based on experience and on the correlation of data obtained from *in vitro* postmortem scanning of radioactive thyroids removed by block dissection of the trachea and other neck structures at necropsy and plastic molds of thyroid glands, re-

moved surgically or at necropsy, containing a solution of radioactive I^{131}. Once the perimeter has been drawn, the area in each lobe in centimeters is determined by a planimeter and the height of each lobe is measured in centimeters. The weight of each lobe is determined separately from the following formula, where k equals 0.323 and is the coefficient of correlation of mean depth and height of a thyroid lobe determined experimentally only for normal or diffusely enlarged thyroid glands. The formula was not developed nor was it intended to be used to calculate the weight of nodular goiters. When nodular toxic goiters are treated with I^{131} a lateral or oblique gammagram is done in addition to the anteroposterior gammagram. From these two views of the thyroid gland a model of the thyroid gland is made from clay, coated with quick-drying rubber or plastic to which radioactive I^{131} has been added. A gammagram is then made of the radioactive simulated thyroid gland. When the silhouette of the patient's gammagram and the simulated thyroid gammagram are identical in size, shape, and appearance, the volume of the clay model is determined and the weight calculated assuming the specific gravity of the thyroid tissue as approximately one.

Weight of lobe = k (area thyroid lobe $cm.^2$ x height of thyroid lobe cm.)

The dose of ionizing radiation that each thyroid gland received has been constant. An attempt was made to deliver 7,000 reps. to every diffuse thyroid gland treated for thyrotoxicosis. This was an arbitrary dose based on our own experience as of 1949, and representing a compromise of the dosage recommended by the Boston and New York groups in the early days of I^{131} therapy for thyrotoxicosis. We have given this thyroid tissue dosage of 7,000 reps. for the past six years to every patient insofar as possible, not primarily because it was felt that this was an optimum dosage but chiefly in order to collect and observe the response of a group of patients receiving the same tissue dose of ionizing radiation. The biologic variation of different persons and glands to ionizing radiation and the nonhomogenous distribution of radioiodine in the thyroid gland were recognized as serious complicating factors. However, it was felt that the problem of radiation sensitivity or radiation resistance could not be approached until the problem of tissue dosage was better understood. This was not possible until more exact methods of the determination of thyroid weight could be established. It was realized that this dosage of 7,000 reps. in all probability would be modified upward or downward, depending upon the results obtained from this investigation or from the experience of others.

No attempt was made to recalculate the tissue dose based on the per cent thyroid uptake of the therapeutic dose in the majority of the cases. It has been reported by several investigators that there is a difference in the concentration of a tracer dose and a therapeutic dose of I^{131}. Differences of 5 to 35 per cent lower have been repeated in the literature[11] but in our experience with the single-channel pulse height analyzer this has not been confirmed. No attempt has been made to adjust the tissue dosage due to any change that might have occurred in the E.H.L. of the tracer dose and the therapeutic dose. Undoubtedly differences will occur but it has been our opinion that there is no reliable method available to detect this change, because with such continual changes taking place in the gland following treatment there would be sporadic unpredictable discharges of radioactivity from the gland as the thyroid tissue was being destroyed. An attempt was made, however, to verify the pretherapy thyroid weight, determined from the tracer dose, with the immediate post-therapy thyroid weight since no difficulty was encountered in having the patient return for a thyroid gammagram 24 to 48 hours following I^{131} therapy.

The oral dosage that will deliver 7,000 reps. to the thyroid gland was calculated from the following Marinelli-Quimby formula:

$$\text{Oral dose in microcuries} = \frac{\text{Reps. x weight of gland x } t\frac{1}{2}}{\text{Max. \% T.U. x E.H.L. x ergs/}\mu\text{c/gm. tissue}}$$

Reps. = 7000

$t\frac{1}{2}$ = physical half-life of I^{131} = 8 days

Ergs/gm = amount of ionizing radiation, assuming there is one microcurie I^{131} uniformly distributed in 1 gm. tissue which remains in the tissue for total decay 144-160 reps.

E.H.L. = effective half-life.

Example: Data obtained from 8-10 day pretherapy diagnostic work-up for each patient:

1) Maximum % thyroid uptake = 75%
2) Weight of thyroid gland = 50 grams
3) Effective half-life = 6 days

TABLE 4

ANALYSIS OF THERAPEUTIC DATA OF 142 CASES OF THYROTOXICOSIS TREATED WITH I^{131} (MEAN VALUES)

	*Pretherapy Thyroid Uptake** (%)	*Pretherapy Effective Half-life (das.)*	*Pretherapy Thyroid Weight*** (Gm.)*	*Reps.*	*Oral dose of I^{131} (mc.)*	*μc./Gm.****
No previous history of thyroid surgery (117)	64.6	6.4	49.9	7,146	4.7	57.7
Previous surgery for thyrotoxicosis (25)	51.7	6.1	22.4	8,360	3.3	77.3
All cases (142)	62.3	6.3	45.1	7,359	4.5	61.2

*Mean normal value: 20%
**Calculated by empirical formula
***Calculated weight
The ranges for these determinations are shown in table 5.

Data already known for all patients:

1) Reps. to be delivered to thyroid gland = 7000
2) Physical half-life of I^{131} = 8 days
3) Reps./μc/gm. thyroid tissue = 160 reps.

$$\text{Oral dose} = \frac{7000 \times 50 \times 8}{75\% \times 6 \times 160} = 3{,}888 \text{ microcuries}$$

Data on Treatment Determined in Pretherapeutic Radioisotope Study

For the purposes of this study, to evaluate better the advantages or disadvantages of a single-dose method of treatment of thyrotoxicosis, and to determine whether there was a mean radiation dosage or range of radiation that would produce an euthyroid state in a thyrotoxic patient, the 107 cases subjected to analysis were divided into two categories: (a) those having had previous thyroid surgery for thyrotoxicosis and in whom a recurrence had developed, and (b) thyrotoxic patients who had no previous surgery but who may or may not have had previous antithyroid therapy. The mean thyroid uptakes determined with the tracer dose of one μc. of I^{131} the mean E.H.L. determined either from the one μc. tracer dose or the thyroid gammagraphic dose, and the mean pretherapy thyroid weight are shown in table 4.

As a general policy the oral dose that would deliver 7,000 reps. to the thyroid gland was determined by using the pretherapeutic tracer data. Of the cases analyzed, 94.4 per cent received 7,000 reps. and only 5.6 per cent received a larger dose of radiation, the average for these six patients being 12,666 reps. Table 4 shows the mean reps. delivered, the mean oral dose of I^{131}, the mean μc. per gram of thyroid tissue as *calculated* from the thyroid weight formula, the mean pretherapy tracer thyroid uptake, and the mean oral therapeutic dose. Table 5 gives the range for these same parameters.

Results of Treatment

A total of 142 patients received I^{131} therapy for the treatment of thyrotoxicosis. One hundred and seven (75.4 per cent) were included for analysis (Table 6). Thirty-five (24.6 per cent) were discarded as unsuitable for analysis at this time, 33 because of inadequate follow-up of less than four months and two because they vomited the therapeutic dose

TABLE 5

ANALYSIS OF THERAPEUTIC DATA OF 142 CASES OF THYROTOXICOSIS TREATED WITH I^{131} (RANGE)*

	Pretherapy Thyroid Uptake (%)	*Pretherapy Effective Half-life (das.)*	*Pretherapy Thyroid Weight (Gm.)*	*Reps. 10^2*	*Oral dose I^{131} (mc.)*	*μc/Gm.*
No previous history of thyroid surgery (117)	19.5-90	3.9-8.5	13.5-211.3	5-21	1.3-23	35.6-135.4
Previous surgery for thyrotoxicosis (25)	17-78.3	2.7-7.8	9.0-69.3	3.5-21	0.8-14.4	33-272
All cases (142)	17-90	2.7-8.5	9.0-211.3	3.5-21	0.8-23	33-272

*Mean normal range: 12.5 — 37.5%

TABLE 6

CASES INCLUDED FOR ANALYSIS OF 142 THYROTOXIC PATIENTS TREATED WITH I^{131}

	Number	*Per Cent*
No history of previous thyroid surgery	84	78.5
Previous surgery for thyrotoxicosis	23	21.5
Total cases for analysis	107	75.4

shortly after administration. The maximum duration of follow-up in the 107 cases included for analysis was 4 years and the minimum duration of follow-up was 4 months (Table 7). Eighty-one (76 per cent) patients were followed 8 months or longer (Table 7).

The results of this single-dose method of treatment in which a mean of 7,146 reps. were delivered to the thyroid gland are shown in table 8.

The number of weeks before the first sign of improvement was noted was determined in 74 (69 per cent) patients. It was found that on the average 3.4 weeks elapsed before a patient noted the first sign of improvement. The time necessary before a patient could resume normal occupational *activity* was analyzed in 53 (50 per cent) patients and found on the average to be 6.6 weeks. Maximum improvement in 21 patients of whom this question was asked was noted on the average at 11 weeks after treatment with I^{131}. Only 16 (15 per cent) of the patients had any exacerbation of their symptoms after treatment. Five (4.6 per cent) had radiation sickness defined as nausea and vomiting 24 hours or longer after therapy. Fourteen (13 per cent) developed varying degrees of tenderness and soreness of the neck or of the thyroid gland.

TABLE 7

DURATION OF FOLLOW-UP

Duration (in mos.)	*Number Patients*	*Per Cent*
4	20	18.8
5-8	43	40.6
9-12	14	13.3
13-14	25	23.5
25-36	2	1.9
37-48	2	1.9

In all the cases analyzed 86.9 per cent were "cured" of their signs and symptoms of hyperthyroidism and 12.1 per cent demonstrated some evidence of continued over-activity of the thyroid.

The cases analyzed more than 4 months after treatment showed an incidence of 8.4 per cent of hypothyroidism. It was of interest that although the "cure rate" improved only slightly at 8 months (89.5 per cent), the incidence of both hypothyroidism (5.8 per cent) and hyperthyroidism (10.5 per cent) was less at 8 months than at 4 months. This lends support to a concept that, if at all possible, patients should not be retreated until approximately 8 months has elapsed from the time of initial therapy.

It was of further interest to find from our analysis that patients having true primary hyperthyroidism with diffuse goiter, and who had previously never received any thyroid therapy of any type (antithyroid compounds within 2 months of I^{131}, surgery or iodides), had a higher response rate of (93 per cent). This suggests that for the best response to I^{131} therapy the antithyroid compound should be discontinued at least 2 months before the diagnostic "work-up" for I^{131} therapy is initiated.

Discussion

In order that this investigation might be conducted in as scientific a manner as possible, the entire study followed a definite

TABLE 8

RESPONSE OF 107 CASES OF THYROTOXICOSIS FOLLOWING SINGLE DOSE I^{131} THERAPY

	*4 mos. After Treatment**		*8+ mos. After Treatment*		*All cases 4+ mos. After Treatment*	
	Number cases	*%*	*Number cases*	*%*	*Number cases*	*%*
Euthyroid	12	57.7	72	83.7	84	78.5
Hypothyroid	4	19.0	5	5.8	9	8.4
Hyperthyroid	4	19.0	9	10.5	13	12.1
Unknown	1	4.8	0	0.0	1	0.9
Total	21		86		107	

*Cases followed *only* 4 mos.

printed, prearranged protocol and every patient was managed and followed in the same way. Case histories, clinical, and laboratory data were not reviewed in retrospect nor were questionnaires used to collect post-therapy information concerning the patient's progress. Every patient was seen before and after treatment by the same physician or physicians at 3 weeks, 6 weeks, 4 months, 8 months, and yearly thereafter. The primary purpose of the study was to try to determine whether or not tissue dosage could be calculated with any degree of accuracy, if the various factors affecting the determination were as carefully controlled as humanly possible, fully realizing that certain factors such as isotope distribution and radiation sensitivity or resistance could not be measured. Certainly these latter variables could not be studied until the problem of tissue dosage had been solved, and the latter could not be precisely determined until a more accurate method of determining thyroid weight was found. It was also for this second reason that this study was undertaken,—to adequately put to the clinical test the empirical formulae for the determination of thyroid weight.[3]

The 10 days of pretherapy diagnostic work-up that are required to determine the thyroid uptake, E.H.L., thyroid weight and to calculate the therapeutic oral dose is not unreasonable and certainly does not unduly delay therapy. This period of time, when added to the post-therapy time of 6.6 weeks required for patients so treated to return to normal occupational activities, is no longer and is comparable to the preoperative antithyroid-Lugol preparation and postoperative convalescence period of surgically treated patients.

A general review was made of the current literature[12-17] and comparison made of our data with data from Radioisotope Services of the V.A. Hospitals in Minneapolis[18] and Boston[19] where a similar protocol was followed, with the one exception that the thyroid weight was *estimated by palpation* rather than by an empirical formulae. It was of interest to note (Table 4) that the single mean oral dose (4.5 millicuries) in our study was considerably smaller than others described in the literature. This might account for the lower incidence of hypothyroidism (8.4 per cent) but would not account for the increased "cure rate" (86.9 per cent). This apparent paradoxical observation in our opinion can possibly be explained on the fact that the oral dosage and hence tissue dosage was more precisely calculated in our series and that this was due primarily to the more accurate determination of thyroid weight and to a lesser extent to the actual determination of the E.H.L. and serial pretherapy thyroid uptake studies since these latter studies were also done in the Minneapolis and Boston V.A. Hospitals.

It has been generally concluded in the literature that because the exact weight of the thyroid gland could not be determined there was very little reason for the physician to attempt to treat a thyrotoxic patient with I^{131} with any degree of accuracy. Thus many methods of treatment with I^{131} have evolved. There are a few investigators[20,21] who have expressed considerable doubt that the thyroid weight can be accurately determined, while others[22] find the empirical formulae reasonably accurate. Himanka[21] reported on the correlation between the frontal projection as determined by direct vision and the volume of the thyroid gland in 44 necropsy cases and found an average error of ± 20 per cent as compared to ± 10 per cent reported by Allen, and a correlation coefficient (k) of 0.33 as compared to 0.323. We fail to see any significant difference in his results when one considers the difference of the thyroid silhouette as determined by direct vision and by the thyroid gammagram.

We have not only found the empirical formulae very helpful in calculating the initial pretherapy thyroid weight but it has been of

TABLE 9

PERCENTAGE CHANGE OF CLINICAL—LABORATORY DATA (MEAN 106 CASES) AFTER TREATMENT WITH I^{131}

Response	*Thyroid Uptake (%)*	*Thyroid Weight (Gm.)*	*P. B. I. (μgm. %)*	*B. M. R. (%)*	*Cholesterol (mg. %)*	*Body Weight (lbs.)*	*Pulse (per min.)*
Euthyroid (84 cases)	—49	—54	—56	—105	+ 9	+10	—22
Hypothyroid (9 cases)	—89		—80	—167	+86	+16	—31
Hyperthyroid (13 cases)	—10	—32	—23	— 42	+20	0	— 6

considerable usefulness in determining the amount of thyroid tissue destroyed or "removed" by radiation. In our experience (Table 9) if 54 per cent of the gland was destroyed, as determined by the pre- and post-therapy thyroid gammagram, a satisfactory response or "cure" was obtained. It is of interest to note that those who failed to respond to a single dose had only 32 per cent of the thyroid tissue destroyed. This observation of post-treatment thyroid weight reduction as an objective sign of favorable or unfavorable response to therapy has been found more reliable than the change in radial pulse or change in body weight. It should be emphasized, however, that the use of the empirical weight formula is limited to determination of thyroid weight in diffuse toxic goiters only and was not intended to be used for thyroid weight determination in either nodular toxic goiters or recurrent postoperative thyrotoxicosis.

Summary

1. A single dose method for the subtotal removal of the thyroid gland with I^{131} for the treatment of diffuse hyperthyroidism has been discussed.

2. The preliminary results of four years experience in the treatment of 142 patients utilizing this single dose method are reported.

3. This single dose method has resulted in the administration of a smaller oral dose of I^{131} and in a higher "cure" rate (87 per cent) than is reported in the literature. Hypothyroidism developed in 8.4 per cent.

4. Data presented suggests that the increased "cure" rate and the lower rate of hypothyroidism may be due to a more accurate calculation of thyroid tissue dosage.

5. It is felt that the increased accuracy of tissue dosage calculation was due primarily to a more accurate calculation of thyroid weight determined from the thyroid gammagram and an empirical formula.

6. Reduction in thyroid weight following therapy was found to be a reliable criterion for determining response to thyroid therapy.

7. Data presented suggests that the male thyrotoxic patient requires a smaller dose of ionizing radiation to effect an euthyroid response.

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Discussion (Abstract)

Dr. Norman H. Garrett, Greensboro, N. C. Dr. Allen emphasizes that the single dose cure of hyperthyroidism is a goal we should all strive for. He has very scientifically set up a protocol and followed it to the letter to determine if a single dose "cure" is a predictable outcome. All variables are accounted for and applied to a standard formula to determine the dose. With this he has had a single dose cure rate of 87 per cent. The ultimate cure is naturally, a theoretical 100 per cent, but single dose cure is an ideal goal.

Our experience at Duke Hospital was recently summarized, with 107 patients treated with I^{131} and adequately followed up. This includes about 80 patients with diffuse goiter. I believe diffuse and nodular goiters should be considered separately. My comments will be limited to hyperthyroidism with diffuse goiter.

The oral dose of RAI in our series was determined by a combination of the Marinelli-Quimby formula, attempting to deliver 6 to 8,000 reps. and adding or subtracting up to one millicurie in light of the clinical condition.

The only variable scientifically determined was the 24 hour uptake of a tracer dose of RAI. The biologic half-life was assumed to be six days and the gland weight was clinically estimated by palpation. Over a period of time we became quite adept at arriving individually at nearly the same estimated weight for any given patient. If our estimation was in error, it at least was constant and fairly reproducible in our group.

Analyzing only the 80 patients with diffuse goiter, we determined the dose in microcuries actually taken up by each gram of thyroid. Sixty microcuries seemed to be the dividing line. Above this nearly all were cured, below this single dose failures appeared. Below 35 microcuries on initial therapy nearly all results were failures.

The figure of 60 microcuries to each gram coincides with the figure Dr. Allen has given us.

The incidence of hypothyroidism in our series was about 4 per cent. These 4 patients developed hypothyroidism after a single treatment. The dose delivered was small in microcuries per gram. We can find no factors that might have warned us of this outcome. We must assume some unusual degree of sensitivity to RAI was present. It is an interesting observation that immediate post-treatment hypothyroidism will frequently disappear without treatment and the return to the euthyroid state be as late as 8 months after therapy. While on the subject of myxedema, it is noteworthy that the incidence after RAI is certainly no greater than after subtotal thyroidectomy in hyperthyroidism.

Another observation that has been made is the apparent inability to produce myxedema in nodular toxic goiters. To my knowledge all reported hypothyroidism induced by RAI has been in diffuse goiters.

Multiple dose treatment poses many problems. We have observed that once initial treatment has failed to effect a cure because it was too little, the ultimate curative dose was significantly higher than one would expect. This implies progressive radioresistance.

Multiple dose treatment also removes one of the distinct advantages of RAI therapy, namely the speed of recovery. Considering the time from the onset of treatment to the return to normal health, RAI is by and large the most speedy means of cure, if cure is obtained by a single dose.

The problem of antithyroid drugs before, during or after RAI treatment has been discussed by Dr. Allen. We believe that ideally antithyroid drugs should not be employed when RAI is to be given. Only 4 of our patients received antithyroid treatment immediately after therapy and, although they received a very adequate dose, their single dose did not effect a cure. Antithyroid therapy is very seldom needed for control on an emergency basis.

The gammagram is a valuable adjunct to the estimation of thyroid weight. With a standardized technic, it will allow compilation of all data from all workers on a common ground. The wide variation in the average therapeutic dose of RAI reported by various authors means that a lot of us may be making significant errors in estimated thyroid weights, even though the individual error must be constant with each group. The gammagram is a refinement that should be more widely used and understood; it will make single treatment cures more predictable. But even those of us without this equipment now should definitely strive for single treatment cures rather than multiple small doses, if RAI is going to keep one of its main advantages, namely simplicity and speed. When single dose cure is attained in the percentage Dr. Allen has shown us, I believe it will undoubtedly be the treatment of choice for hyperthyroidism with diffuse goiter.

Dr. S. B. Nadler, New Orleans, La. (Closing). I was very much interested in listening to these experiences; the reassuring part about coming to these meetings is to find other people are having about as much trouble as you are having at home.

I enjoyed Dr. Allen's paper very much. The chief point that has been underemphasized is the clinical evaluation of the patient. I should like to emphasize this again. No matter how scientific one becomes, one must remember that patients are variable biological creatures. This has been very forcibly brought to our attention. In our series of approximately 100 cases as of two years ago, we had 9 cases of hypothyroidism; 7 of those 9 patients had received only one dose of radioactive iodine. We were forced to the same reluctant conclusion that Dr. Garrett has made that there must be some biologic variation in the radiosensitivity of the glands of different people, because some people received single doses that were twice as large and did not become permanently hypothyroid.

Another point to be emphasized from the clinical standpoint is that instances of toxic nodular goiter may exhibit low uptakes, just at or slightly above the upper range of normal and yet may be very toxic clinically, whereas patients with diffuse goiter may have an uptake of 85 or 90 per cent and not be as toxic as the patients with nodular goiter. What are we to do about these patients? Not much has been said here about nodular goiter and single doses. In our experience, it has taken single doses of from 10 to 20 millicuries to take care of a nodular goiter in some instances. There is a vast difference between toxic nodular and diffuse goiter from the standpoint of therapeutic level. We, too, have used the guess palpation method and have ended up with fundamentally the same results, namely, a group of unexpected hypothyroid patients.

Dr. Garrett pointed out that one may vary a millicurie up or down, because a doctor sends a patient in from out of town and is not going to send him back several times for treatment. So one gives the patient an extra millicurie, or if one thinks the pa-

tient is anxious about his treatment, one may add an extra millicurie. Thus the desired dose level is 4 millicuries, and one ends up giving 6, a 50 per cent increase in dose. Since the palpatory method may vary by 20 or 25 per cent one is still close to the therapeutic range.

I do not say this to decry the method of gammagram measurement. This is a step in the right direction, but I do not believe that the ultimate solution of the prevention of hypothyroidism or predetermination of the level of a single curative dose is going to depend upon more accurate measurements of the goiter. It would seem that biologic variation is the important limiting factor.

Histologic Changes Produced in the Nonmalignant Thyroid Gland by Therapy*

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MICROSCOPICALLY THE NORMAL THYROID GLAND is made up of acini of about uniform size lined by cuboidal epithelial cells and filled with colloid. The epithelial cells are resting on a thin basement membrane which separates them from the capillaries which surround the acini. The colloid usually has smooth borders and stains uniformly.

In toxic hyperplasia, either diffuse or nodular, the lining cells become columnar and undergo hyperplasia so as to form papillary projections into the lumens of the acini. The colloid has a fuzzy appearance, with areas of vacuolization and scalloping of the edges. Lymphocytic infiltrate and follicle formation are variable.

A rarer variety is characterized by an increase in the number of follicles with a marked increase in the size of the gland. The follicles are small and show little infolding of the epithelium. There is usually a considerable infiltrate of lymphocytes in such glands.

Treatment with iodine alters the appearance of the gland so that the follicular epithelium resumes its cuboidal shape, or may even become flat, and the acini fill with colloid.

The thiourea derivatives have a different effect. They block the organic binding of iodine to form thyroid hormones but show no suppressive effect on the hyperplasia of the gland produced by the continued secretion of thyrotropic hormone of the pituitary gland. The effect of the TSH, if anything, appears enhanced. The cells lining the acini become taller and more hyperplastic forming numerous papillary infoldings. The colloid in the gland is depleted so only little remains as the acini appear to shrink. Propyl- and methylthiouracil have a similar action.

The combination of potassium iodide or Lugol's solution with the thiourea derivatives serves to cause involution of the gland similar to that seen with iodides alone. This causes decreased vascularity and facilitates surgery.

Itrumil (5-iodo 2-thiouracil) has been reported to have a different effect on the toxic gland due to the incorporation of iodine into its molecule. It has been reported[1,2] that it has no goitrogenic activity. It was suggested that the presence of iodine in the molecule causes a high level of circulating iodine in the blood, which suppresses pituitary secretion of TSH, and that it also causes more selective uptake of the molecule by the thyroid. Possibly the compound, after incorporation into the cellular structure of the gland, acts both to suppress hormone formation by its thiouracil fraction and to neutralize the effect of the thyrotropic hormone by its iodine fraction. It was reported, therefore, to have a

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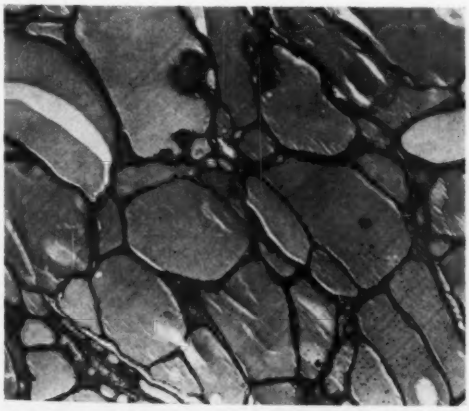
more rapid action than a combination of propylthiouracil and potassium iodide and, in addition, to have no goitrogenic effect.

Recently exception has been taken to such statements by studies done on rats by Vanderloon and Caplon.[3] They found considerable goitrogenic effect and increase in the iodine space in the gland such as is found in rats treated with plain proplythiouracil. There was increased cell height, vascularity and discharge of colloid.

Methimazole[4] acts also by inhibiting the production of thyroid hormone, and hence its histologic effects are similar. However, it has also been reported to have a less goitrogenic effect. I have found no record of studies done on material obtained before iodine was also started as preparation for surgery. After iodine is started, the same involutional changes were found as in cases treated with propylthiouracil and iodine.

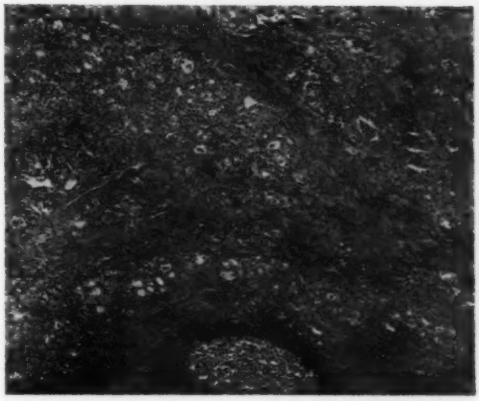
The x-ray has long been used to treat hyperthyroidism with variable results. Histologically the change produced may be that of simple involution (Fig. 1). Pemberton[5] stated that Broders was unable to distinguish irradiated from nonirradiated thyroid tissue. The amount of radiation used is from 1,200 to 1,800 r. This may affect primarily the hyperplastic epithelial cells and the lymphoid tissue, causing involutional changes and occasional atypical cells. Larger doses of radiation may produce changes of acute necrosis,

FIG. 1



Patient was sensitive to propylthiouracil and had a B.M.R. of plus 40. She received 1,200 r of x-ray two months prior to operation and also received iodine in preparation. Note only small residual area of hyperplasia in otherwise normal appearing gland.

FIG. 2



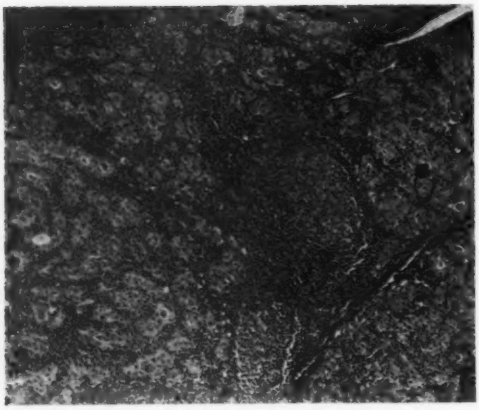
Twenty-three year old white man who had initial B.M.R. of plus 75 and received a total of 51.6 mc. of I^{131} in divided doses over period of 8 months; symptoms persisted and he was placed on potassium iodide, and thyroidectomy was done. Note presence of Hurtle type cells, fibrosis and lymphocytes.

follicular atrophy, and marked fibrosis. Glands in the way of radiation administered for adjacent malignancies may show such pronounced changes.

Toxic or normal[6] glands treated with radioactive iodine (I^{131}) may show similar changes of necrosis, atrophy, and fibrosis following radiation. There is noted a high incidence of glands having an appearance similar to that of Hashimoto's disease if they have been removed more than six months following treatment. The presence of the large Hurtle cells, fibrosis, and lymph follicle formation may be seen (Fig. 2). The Hurtle cells are thought to represent the effect of the continued stimulation of the TSH on an involuted or atrophic gland.

Thyroiditis. This is a difficult disease in which to evaluate the histologic effects of therapy since there is no uniformity of nomenclature and serial biopsies have not been done routinely. The only report I could find on such work was that of Crile and Furr[7] who reported on 62 cases of struma lymphomatosa treated with desiccated thyroid, ACTH, cortisone, x-ray, or combinations of these. Initial and serial biopsies were taken. Since the cause of the disorder is not known, the possible mechanism of action of these agents can only be presumed. Desiccated thyroid may exert its effect by suppressing TSH production or by changes in the production of lymphoid moderating hormone. It is presumed that

FIG. 3



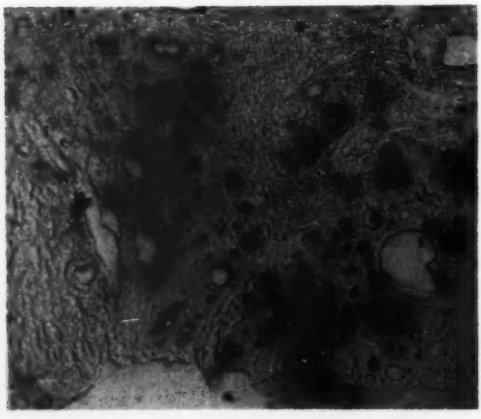
Struma lymphomatosa. Note numerous Hurtle cells, fibrosis, lymphocytic infiltrates, and lymph follicle formation. Lymphocytic areas respond to treatment with lympholytic agents such as cortisone, ACTH, and x-ray. Areas such as these function poorly.

there may be an excess of TSH in struma lymphomatosa.

The action of cortisone may be similar to that of x-ray therapy, producing lymphocytolysis. ACTH and cortisone were found most active in producing acute involution, since the enlargement is usually due primarily to lymphocytic infiltrate and follicle formation (Figs. 3 and 4).

The same agents have been reported to produce some improvement in cases of acute nonsuppurative thyroiditis (subacute thyroiditis of Crile).

FIG. 4



Autoradiograph from an area showing good function in a case of struma lymphomatosa. Such foci may account for high I^{131} uptake in a gland made up mostly of poorly functioning Hurtle cells and lymphocytes.

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Discussion (Abstract)

Dr. John Beach Hazard, Cleveland, Ohio. I have enjoyed this paper very much and it was especially a pleasure to see those very fine photomicrographs of the effects of radiation. Some have stated that radiation may actually produce the lesion, struma lympho matosa. I would agree with Dr. Fink that though the oxyphilia seen in struma lymphomatosa may be present, the general background is not truly of that disease. There is irregular fibrosis; the follicles, though small, are not separated by a dense lymphocytic infiltration, and the lymph follicles, though they may be present, usually are not numerous. So I do not believe it is truly struma lymphomatosa.

The results we have seen in the illustrations of this paper represent mostly the effect of drugs on the gland. As you all know the thyroid is an organ which particularly is susceptible to many chemical compounds, many of them goitrogens, whether they be food or otherwise. It is one of the commoner areas in the body for iatrogenic disease.

One of the drugs which is used to treat a thyroid disorder also may give rise to goiter, and that is iodide, when given in excessive doses. Dr. Turner has a paper shortly after this in which he will discuss such an effect at some length. The thiouracil effects have been quite interesting. Experimentally, as you know, there has been at least one report in which a lesion very closely resembling struma lymphomatosa has been produced by giving thiouracil to rats over a period of some 600 days. About 25 per cent of these animals revealed lesions similar to struma lymphomatosa.

That brings to mind the possibilities in the human of the use of thiouracil for a long period of years. I have not seen thyroid specimens from individuals who have been given thiouracil for four, five or six years. The early changes as I showed today, and as you have seen from Dr. Fink's presentation, are marked hyperplasias which sometimes can be almost tumorous; the differentiation between the pseudopapilliferous proliferations due to thiouracil and papillary carcinoma may at times produce a real challenge. However, the fact that these changes are diffusely distributed, so there are no areas in which one can separate them from normal foci of thyroid, usually serves to separate this lesion from true neoplasm.

As far as the effect of radiation is concerned, there is another point that came to mind when I was listening to this paper,—that is the effect of radiation on the thyroid as incidental to treatment of the enlarged thymus. Several have emphasized the fact that carcinoma of the thyroid is of increased incidence in individuals who have had such previous radiation.

Regarding the effect of ACTH on the thyroid with subacute thyroiditis, we have really very little information. Several years ago, we had occasion to observe just one instance in which there was a biopsy after this hormone had been used and there appeared to be some reduction in the infiltrating cells but, after all, estimations from small biopsies are not sufficient to give absolutely accurate results for such comparison, and such a single observation can only indicate a possible response. Certainly one might expect that there would be an associated reduction of inflammatory reaction.

Actually, so far as we are concerned with these drugs, we are dealing with agents which are specific, and are pharmacologically powerful. I think, in all instances when one is dealing with such substances, there must be a continuous lookout for associated iatrogenic disorders. The thyroid is an organ in which this appears particularly necessary. I greatly enjoyed Dr. Fink's very fine presentation.

Dr. Fink (Closing). I do not know that I have anything further to add. I would like to mention one thing I forgot to say when I was showing the slides. The hyperplasia seen in the patients treated by thiouracil, or thiouracil derivatives is really due to the effect of the anterior pituitary. In rats they can produce hyperplasia similar to that seen in humans following propylthiouracil, and then change the gland to an involuting type of gland, filled with colloid and having an acini lined with cuboidal epithelial cells, by removing the pituitary. The gland then goes back to forming colloid similar in appearance to the normal gland, but the colloid, since the rats are still receiving propylthiouracil, does not contain iodine. We have the effect of blockage of the hormone formation by the thiourea derivative, yet with the normal appearance of the gland. So maybe the hyperplastic effect does come from the anterior pituitary.

Goiter Induced by Iodide in Children*

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INCREASING ATTENTION is being directed toward the clinical response of the thyroid gland to excessive amounts of iodide. There is considerable evidence from experimental and clinical investigations that the presence of an excess of iodide interferes with the thyroidal synthesis of organically bound iodine, although the mechanism by which this inhibitory action is effected is a subject of controversy.[1-3]

Experimentally, there is adequate proof from *in vitro* studies that I^{127} in amounts of 20 to 50 micrograms inhibits the conversion of iodide to thyroxine,[4] and that in amounts above the optimal concentration of 10^{-3}M this inhibition is due to the competition of the excess iodide with tyrosine for the molecular iodine of the gland.[5]

In animal experiments, using tracer doses of I^{131}, the organic binding of potassium iodide administered was found to progress normally only when serum iodide levels were less than 30 to 35 micrograms per 100 ml.[6] It was later found that with a total serum iodide concentration of 20 micrograms per 100 ml., organic binding was not maintained for more than twenty-six hours and declined after fifty hours.[7] This escape of the normal thyroid from iodide-induced inhibition has been further confirmed by metabolic studies in which the inhibitory phase was characterized by a fall in basal metabolic rate (B.M.R.), which was associated at its lowest point with the presence of thyroidectomy cells in the pituitary. After discontinuing large doses of iodide, the B.M.R. showed a marked rebound in its return to normal.[8]

These observations of the blocking effect of iodide on thyroid function are borne out by clinical investigations. In short-term human studies, inhibition of organic binding of iodine has been observed in euthyroid subjects when serum levels of iodide exceeded 6 to 12 micrograms per 100 ml., and in thyrotoxic patients at concentrations of 5 micrograms per 100 ml. or less.[9] Another study, in

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which I^{127} was used as a stable carrier, showed that in most of the patients with exophthalmic goiter the extrarenal disposal rate of I^{131} was reduced to euthyroid levels when the serum concentration of iodide exceeded 1.0 mg. per 100 ml., and could be reduced further to almost zero when the serum concentration reached 10.0 mg. per 100 ml. The iodine-trapping function of the gland was suppressed at serum concentrations of 0.2 mg. per 100 ml., and at 5.0 mg. per 100 ml. (or less) synthesis was suppressed.[10]

The appearance of goiter and/or myxedema or the exaggeration of pre-existing goiter have been attributed to administration of iodide in several reported cases. Hurxthal[11] described a 6 year old girl with asymptomatic goiter who had been given Lugol's solution over a long period of time during which the goiter grew larger, the B.M.R. fell to -21 per cent, and the level of serum cholesterol rose to 432 mg. per 100 ml. There was clinical evidence of myxedema. Within less than one month after the withdrawal of iodide, the serum cholesterol level was reduced to 179 mg. per 100 ml., signs of myxedema disappeared, and the goiter decreased in size. No desiccated thyroid had been given. The patient of Raben[12] was a 41 year old woman in whom goiter of three months' duration was believed to have resulted from the use of Lipiodol in a bronchogram. Clinically, the patient appeared myxedematous. Serum cholesterol concentration was 405 mg. per 100 ml. and the results of I^{131} studies were indicative of myxedema. After three months' treatment with desiccated thyroid, 3 grains daily, the goiter regressed completely, as did the clinical symptoms of hypothyroidism. The thyroidal radioactive iodine uptake remained in the myxedematous range and the serum cholesterol level was still elevated to 219 mg. per 100 ml.

In 1952, Bell[13] reported four patients, all of whom had goiter; three also had myxedema. Three of the four patients were asthmatics who had had treatment with iodide for varying lengths of time. In the other the goiter was attributed to pregnancy and the patient received Lugol's solution for seven years, during which time clinical and laboratory signs of myxedema appeared. Thyroidectomy (subtotal) was performed in only one patient, an 11 year old asthmatic girl. Histologically the specimen showed colloid storage goiter. Continued iodide therapy postoperatively resulted in myxedema, which was controlled by iodide withdrawal and administration of a half grain of desiccated thyroid daily. In the three patients presenting goiter with myxedema, serum cholesterol levels were initially elevated and the basal metabolic rates were depressed. After stopping iodide therapy and starting the administration of desiccated thyroid for periods of two to six months, serum cholesterol concentration decreased to normal in two of these patients and remained moderately elevated in one. During this period of treatment with thyroid the goiters regressed markedly in size. The fourth patient, without signs of myxedema, was treated by discontinuing iodide. No desiccated thyroid was given. After two months the Grade II goiter had decreased in size by half, and at nine months was not palpable.

In the two myxedematous patients of Morgans and Trotter,[14] iodide was considered to be the causative agent; one of these patients, an asthmatic, had goiter. In both, the serum cholesterol levels were elevated and thyroidal I^{131} uptake studies indicated myxedema. The basal metabolic rate was not significantly depressed, however. In each instance, repeated withdrawals of the iodide were correlated with disappearance of the clinical and laboratory signs of myxedema, and reduction in the size of the goiter. No thyroid hormone was given. Readministration of the iodide was associated with recurrence of the myxedema and increase in size of the goiter. It is of interest that with each withdrawal of the iodide, the thyroidal I^{131} uptake showed a well-defined increase to levels approaching those seen in thyrotoxicosis, but fell to normal within a few weeks. An autopsy was performed on one of these patients, and the thyroid histologically showed colloid storage.

Additional evidence that prolonged administration of iodide has a goitrogenic effect has been presented by Turner and Howard,[15] who reported the occurrence of goiter and varying degrees of hypothyroidism in 13 young asthmatics aged 5 to 17 years, all of whom had received iodide for periods of several months to several years. There were 7 boys and 6 girls in the group. In all 13 patients, thyroid enlargement was apparent and

ranged from Grade II to more than Grade III. Seven of the 13 subjects presented clinical and laboratory evidence of myxedema. Cessation of iodide therapy followed by administration of desiccated thyroid resulted in marked regression in the size of the goiters or their complete disappearance, and routine determinations of thyroidal I^{131} uptake, urinary I^{131} excretion, and serum levels of protein-bound iodine showed a significant return toward normal values.

The purpose of this communication is to report the further progress of three of these patients and to present three additional asthmatic patients with asymptomatic goiter who were treated by withdrawal of iodide, but who received no form of thyroid therapy.

Case Reports

Case 1. D. J., a seven and a half year old asthmatic white boy, had been treated with syrup of hydriodic acid, three-quarters of a teaspoonful twice daily for 5 years, excluding the summer months. The total daily dose of iodine had been 105 mg. There had been no weight loss. Thyroid enlargement had been noticed three months previous to examination.

At the time he was seen by us, his weight was 52 pounds, height 48½ inches, blood pressure 90/70, and pulse 100. The thyroid was diffusely enlarged (Grade II) and was smooth and firm. The hemogram was normal. The 24 hour thyroidal uptake of radioactive iodine was 3.4 per cent and urinary excretion, 90.1 per cent. The level of serum cholesterol was 186.6 mg. per 100 ml. and of serum protein-bound iodine, 16.1 μg. per 100 ml. A roentgenogram of the chest showed substernal extension of the thyroid. The bone age was normal.

Iodide was discontinued and desiccated thyroid (a half grain daily) was prescribed. The dose of desiccated thyroid was increased to 1 grain daily after one month. After six months of treatment, the boy had gained 3 pounds in weight and had grown 2½ inches. There was tachycardia, a blood pressure of 100/70, and a pulse of 100, probably due to the fact that he was taking ephedrine for an asthmatic episode. The thyroid had regressed in size to Grade I status. Thyroidal radioiodine uptake at this time was 11.7 per cent and the urinary excretion, 74.5 per cent. The level of serum cholesterol was 141 mg. per 100 ml. and of protein-bound iodine, 8.6 μg. per 100 ml.

One year after iodide therapy had been replaced with desiccated thyroid, the weight gain was 6 pounds and the height increment, 3½ inches. The thyroid was less than Grade I in size. Thyroidal radioiodine uptake was 12.6 per cent. The level of serum cholesterol was 166 mg. per 100 ml., and the protein-bound iodine, 6.6 μg. per cent. Desiccated thyroid was continued for an additional three months, after which time it was stopped. Two months after discontinuing thyroid therapy, and 17 months after discontinuing hydriodic acid, the weight was unchanged, although he had grown three-quarters of an inch. Blood pressure was 90/70 and the pulse was 90. The thyroid was barely palpable and the substernal goiter was no longer detectable roentgenologically. The thyroidal uptake of radioiodine was 36.6 per cent, and the urinary excretion, 54.2 per cent.

Case 2. K. M. was a 10 year old asthmatic white girl who had also been treated with syrup of hydriodic acid, 1 teaspoonful three times daily, over a period of 5 years, with the exception of two or three months each summer. The total dose of iodine was 270 mg. daily. Goiter had been diagnosed after 3 years of treatment with iodide, and 9 months later she had been given desiccated thyroid (1 grain daily) and Lugol's solution (10 drops daily). Her total iodide intake then had been 270 mg. in the syrup of hydriodic acid plus 126 mg. of iodine in the Lugol's solution, or a total of 396 mg. per day. The desiccated thyroid had been discontinued 11 months later, but she had continued to take the Lugol's solution and hydriodic acid. As there had been no improvement in the goiter, thyroidectomy was advised but was not performed.

When the girl was first examined by us her weight was 79 pounds and height, 56½ inches. Blood pressure was 90/70 and the pulse was 100. The thyroid was found to be diffusely enlarged (Grade III), smooth, moderately firm, and horseshoe shaped. No laboratory studies were made until 30 days after cessation of all medication. After the 30 day period of iodide deprivation, the findings on urinalysis and the hemogram were normal. The B.M.R. was +13 per cent. Thyroidal radioiodine uptake was 14.3 per cent and urinary excretion 64 per cent. The level of serum cholesterol was 260 mg. per 100 ml. and of protein-bound iodine 14.4 μg. per 100 ml. The bone age was normal.

Desiccated thyroid was begun with a dosage of a half grain daily, and in four weeks this was increased to one grain daily. Five months later there had been no weight gain, although there had been an increase of two inches in height. Blood pressure was 120/80 and pulse 100. The thyroid was barely palpable (Fig. 1). Thyroidal radioiodine uptake was 11.6 per cent, and urinary excretion was 68.1 per cent in twenty-four hours. The level of serum cholesterol was 177 mg. per 100 ml. and protein-bound iodine was 5.7 μg. per 100 ml. Thyroid therapy was withdrawn one month later. Eleven months after cessation of desiccated thyroid and after 9 months of no iodide therapy, this patient was free of goiter, had gained 13 pounds, and had grown 3¼ inches. She was entirely asymptomatic.

Case 3. G. T., a 17 year old white boy, had taken syrup of hydriodic acid, 1 teaspoonful three times daily, almost continuously for 5 years. Thyroid enlargement became apparent during the last few months of iodide medication. For a period of 2 years prior to his first visit to us he had taken no iodide and had been free of asthma, but thyroid enlargement had been progressive and there had been difficulty in swallowing.

At the time of his first visit he weighed 168 pounds and was 71 inches tall. Blood pressure was 110/70 and pulse, 60. The thyroid was diffusely enlarged (Grade III), horseshoe shaped, and very firm. The B.M.R. was -3 per cent and the level of serum protein-bound

iodine was 5.3 μg. per cent. Thyroidal uptake of a tracer dose of 15 microcuries of radioiodine was 41.2 per cent in 24 hours. Another tracer study 10 days later was reported as showing an uptake of 44.2 per cent.

Thyroid hormone therapy was begun in an attempt to decrease the size of the thyroid. During the following four months, l-thyroxine was administered in increasing dosages up to 400 mg. daily. The thyroid enlargement regressed only very slightly. At the end of this 4 month period the weight was unchanged, blood pressure was 90/70, and the pulse was 56. Thyroidal uptake of radioiodine was 6.8 per cent, and urinary rate excretion was 82.5 per cent in 24 hours. Desiccated thyroid was now prescribed (6 grains daily) and the l-thyroxine was continued. Two months later there was no clinical improvement and thyroidectomy was performed. The histopathologic diagnosis was struma lymphomatosa.

The three patients described next had similar histories and laboratory findings but were treated only by discontinuing iodide. Thyroid hormone was not administered.

Case 4. S. S., an asthmatic white girl, aged seven and a half years, had been treated with syrup of hydriodic acid, 1 teaspoonful (70 mg.) daily during a period of four and a half years. Treatment had been irregular during the summer months. Goiter had been observed by her physician 3 months prior to referral to us, at which time she had been taking iodide without interruption for 10 months. Her school work had been satisfactory.

Upon examination, the patient was found to be a tall, thin child, 51 inches in height and weighing 49 pounds. Blood pressure was 80/60 and the pulse was 80. Upon palpation, the thyroid was found to be diffusely enlarged (Grade II), smooth, and moderately soft. Clinically, the child appeared to be euthyroid. Thyroidal I^{131} uptake was 3.2 per cent and renal excretion was 76 per cent.

All medication was withdrawn and the patient was seen six weeks later. At this time the thyroid enlargement had decreased (Grade I). Thyroidal I^{131} uptake had risen from 3.2 per cent to 21.5 per cent. Fourteen weeks after stopping iodide and with no thyroid therapy, her height was 51¼ inches, weight 53 pounds, blood pressure 90/70, and pulse 78. The thyroid was barely palpable and thyroidal I^{131} uptake was normal at 27.4 per cent; the excretion was 61 per cent.

Case 5. R. W., an alert asthmatic white boy, aged 5 years, had been taking saturated solution of potassium iodide, one-half teaspoonful (1,664 mg. of iodine) daily for two and a half years. Thyroid enlargement had been noticed two and a half months previously by his physician.

Upon examination, his height was 42½ inches (average for his age) and weight 35 pounds (6 pounds below the optimum). Blood pressure was 70/50, and the pulse 70. The thyroid was diffusely enlarged (Grade II), and was moderately firm. After administration of 5 microcuries of I^{131}, the thyroidal uptake was 2.8 per cent and the excretion was 85 per cent.

Potassium iodide was discontinued and no other medication given. After seven weeks, the thyroid was half its former size and much softer. Thyroidal I^{131} uptake was 3.1 per cent. Eleven weeks after withdrawal of iodide, the I^{131} uptake had risen only to 4.1 per cent. At this time the level of serum cholesterol was 188 mg. per 100 ml. and of protein-bound iodine, 6.2 μg. per 100 ml. At the end of 5 months, the boy had grown one inch in height and had gained 4 pounds. The thyroid had regressed to normal size. Thyroidal I^{131} uptake was 14.4 per cent and excretion was 76.4 per cent in 24 hours. The level of serum cholesterol was 190 mg. per 100 ml. and of protein-bound iodine, 6.8 μg. per 100 ml.

Case 6. D. S. was a 10 year old white boy who had been taking a prescription for asthma for the previous 14 months. During this period he had gained 24 pounds in weight with little or no increase in height. The parents had noticed an increase in physical and mental sluggishness for 6 months. Two weeks prior to our examination his physician had observed thyroid enlargement.

Upon examination, his weight was 81 pounds and height 51 inches. Blood pressure was 70/40 and pulse 60. He was somewhat obese, the complexion was sallow and the skin was dry. The thyroid was enlarged (Grade III), smooth, and moderately soft. There was a rather heavy growth of hair over the lumbar area. Roentgenograms showed his skeletal age to be approximately 8 years. The laboratory reported hyperchromic anemia. The level of serum cholesterol was 414 mg. per 100 ml., of protein-bound iodine 14.5 μg. per 100 ml., and of inorganic iodine about 500 μg. per 100 ml. Qualitative tests showed iodine in the urine. After the administration of 15 microcuries of radioactive iodine, the thyroidal uptake was only 2.8 per cent and urinary excretion was 82.9 per cent in twenty-four hours.

The medication for asthma was discontinued and no other treatment was prescribed. Five weeks later the boy had lost 9 pounds. Blood pressure was 100/70 and the pulse was 80. He was much more alert. The goiter had decreased to about half its former size (Fig. 2). The level of serum cholesterol was 196 mg. for 100 ml. and of protein-bound iodine, 8.6 μg. per 100 ml. Thyroidal uptake of I^{131} was 17.6 per cent and urinary excretion was 71.6 per cent in 24 hours.

Discussion

Study of the six cases reviewed here reveals a consistent pattern (Table 1). All the patients were asthmatics, all had been treated with iodide for prolonged periods of time, and all had goiters. The minimal daily requirement of iodide is reported to be from 30 to 50 micrograms,[16] but some of these children had received an excess of iodide up to 100,000 times the daily requirement (e.g., K. M., Case 2).

There is experimental proof that excessive amounts of the iodide ion inhibit the organic binding of iodine. Clinically, the blocking

action is brought about by amounts in excess of 0.1 mg.[10] In our six patients, the evidence of thyroid derangement, aside from the development of goiter, was borne out by the laboratory data.

It is well known that the thyroidal uptake of I^{131} is significantly depressed and the level of serum protein-bound iodine is increased when excessive amounts of iodide are present in the body. This was evident in two of four patients in whom tracer studies were made during iodide therapy. The thyroidal uptake of radioactive iodine was at very low levels, and ranged from 2.8 to 3.4 per cent in 24 hours.

In two of the subjects, tracer studies were made only after withdrawal of iodide therapy for periods of 4 and 104 weeks. In one instance (Case 2) the uptake was slowly approaching normal (14.3 per cent), although the serum cholesterol and protein-bound iodine levels remained high. In the second instance (Case 3), the uptake by the thyroid (after two years of no iodide) was high, and within the borderline range of hyperthyroidism. The normal serum protein-bound iodine concentration of 5.3 μg. per 100 ml., the lack of clinical signs of thyrotoxicosis and the persistence of the Grade III goiter, suggest that during the two years the thyroid had partly, but not completely, overcome the iodide inhibition. Probably compensatory overproduction of thyrotropin by the anterior pituitary had caused the continued hypertrophy and hyperplasia of the thyroid, as has been pointed out by Crile.[17]

The withdrawal of iodide and the administration of desiccated thyroid to two of the patients (Cases 1 and 2) resulted, within 20 to 52 weeks, in a dramatic change in the size of the goiters to less than Grade I (Fig. 1). This decrease in size was similar to that shown by three of Bell's patients who had goiter attributed to iodide therapy for asthma.[12] During therapy with desiccated thyroid, I^{131} tracer studies showed that the

TABLE 1

Patient	Age Yrs.	Sex	Treatment: Drug	Treatment: Duration in weeks	Treatment: Daily Dose	Grade of Goiter	I^{131} Uptake % 24 hrs.	I^{131} Excretion % 24 hrs.	Serum Cholesterol mg. %	Blood PBI mcg. %	B.M.R. %
1											
(D.J.)	7.5	M	Iodide (SHI)*	260	8 cc.	II	3.4	90.1	186.6	16.1	
			Des. Thyroid	24	0.5 gr.	I	11.7	74.5	141	8.6	
			Des. Thyroid	52	0.5 gr.	<I	12.6		165.6	6.6	
			None	8		<I	36.6	54.2			
2											
(K.M.)	10	F	Iodide (SHI)* + Lugol's	260	15 cc.+ 10 drops	III					
			None	4		III	14.3	64	260	14.4	+13
			Des. Thyroid	20	0.5-1.0 gr.	<I+	11.6	68.1	176.6	5.7	
			None	8		<I	19.7	51.3	194.6	5.1	
			None	11		<I	28.7				
3											
(G.T.)	17	M	Iodide (SHI)*	156	15 cc.	>III					
			None	104		>III	41.2			5.3	−2
			l-Thyroxine	16	300 μg.	III					
			l-Thyroxine		300 μg.+						
			Des. Thyroid	4	6 gr.	III†					
4											
(S.S.)	7.5	F	Iodide (SHI)*	180	2.5 cc.	II	3.2	76			
			None	6		I	21.5				
			None	14		<I	27.4	61		6.1	
5											
(R.W.)	5	M	Iodide (ssKI)	130	2.5 cc.	>I	2.8	85			
			None	7		I	3.1				
			None	11		<I	14.4	76.4	190	6.8	
6											
(D.S.)	10.3	M	Iodide (Unknown)	60	?	II	2.8	82.9	414	14.5	
			None	5		<I	17.6	71.6	260	8.6	

*Syrup of hydriodic acid.
†Thyroidectomy. Histopathologic diagnosis of struma lymphomatosis.

FIG. 1

K. M. (Left) Grade III goiter developed during iodide therapy for asthma. (Right) Less than a Grade I enlargement after taking desiccated thyroid for 5 months.

FIG. 2

D. S. (Left) Grade II diffuse goiter developed during 12 months of therapy with iodide. (Right) Less than Grade I enlargement 5 weeks after stopping iodide and without desiccated thyroid.

thyroidal uptake and urinary excretion of the isotope were in or near the normal range. Serum cholesterol values during treatment with desiccated thyroid were significantly lowered only in one of the two patients, but serum protein-bound iodine values attained normal levels in both patients. In case 3 the treatment was initially with 300 μg. of l-thyroxine daily. The Grade III goiter responded only very slightly during 16 weeks of treatment, although the 24 hour uptake of radioiodine was reduced from 44.2 per cent to 6.8 per cent. This observation is in agreement with that of Starr,[18] who has shown that administration of l-thyroxine can suppress the thyroidal uptake of radioactive iodine. The patient showed no further response, although in addition to the l-thyroxine he received 6 grains of desiccated thyroid daily for four weeks. Thyroidectomy was performed and microscopic examination of the thyroid gland showed struma lymphomatosa.

In two patients (Cases 4 and 5) the goiters regressed to nearly normal size within 11 to 14 weeks after discontinuance of iodide therapy and without the administration of thyroid hormone (Fig. 2). The thyroidal uptake of radioactive iodine was within normal limits, although a slight initial increase in uptake, such as was described by Morgans and Trotter[14] was indicated in one instance (Case 4). Urinary excretion of the tracer dose fell moderately. In three patients (Cases 4, 5, and 6) who did not receive any form of thyroid medication after discontinuing iodide, the Grade I to II goiters diminshed in size to less than Grade I.

Conclusion

In view of the clinical evidence and the convincing experimental proof of the antithyroidal and goitrogenic effect of an excess of iodide, it would appear that the occurrence of goiter, hypothyroidism, or both, in association with prolonged iodide therapy is not merely coincidental. The incidence of this "paradoxical" effect of iodide is low in asthmatics and other patients being treated with iodides. However, regardless of the mechanism, the inhibitory action does occur in a rather limited group of individuals who are unable, for some reason, to compensate and overcome the blocking effect of excess iodide ion.

The evidence derived from the development of struma lymphomatosa in case 3 seems to indicate that the iodide-induced change may proceed uninhibited. The antithyroidal effect of iodide can be abolished by the administration of thyroid, although it has been shown that the mere cessation of iodide therapy will reverse the change in a majority of patients.

Summary

1. Six asthmatic children have been described in whom development of goiter was attributed to prolonged treatment with iodides.

2. Significant depression of the thyroidal uptake of radioactive iodine was associated with definite elevation in the level of serum protein-bound iodine. Serum cholesterol levels were increased to moderate or to high levels.

3. Following the withdrawal of iodide in two patients, and subsequent treatment with desiccated thyroid, there was a regression in size of the goiters and a return to normal values for both thyroidal uptake and urinary excretion of radioactive iodine. Serum protein-bound iodine levels also returned to normal.

4. Withdrawal of both iodide and desiccated thyroid was not followed by recurrence of the goiters and the thyroidal I^{131} uptake and serum protein-bound iodine level remained normal.

5. The inhibitory effect of excess iodide on the thyroid in one patient was not reversed by prolonged deprivation of iodide or by administration of thyroid hormone.

6. In three patients, following only discontinuance of iodide without institution of thyroid therapy, the goiters regressed to normal or nearly normal size.

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Discussion (Abstract)

Dr. John L. Goforth, Dallas, Tex. First of all, I want to comment on the general excellence of this joint symposium, or attack on the thyroid. I feel that the Program Committee is certainly to be complimented for bringing to us this excelllent program and I cannot help but say that when clinicians and pathologists get together everyone benefits.

In reference to Dr. Turner's paper, I think this is an important contribution. Studies of this type emphasize the very practical observation that medications given today for specific favorable effects may produce unfavorable long-range results which may not be apparent for months or even years. For example, antibiotics, hormones, maybe transfusions, and other medications, which may be taken orally or by injection, either intravenously, subcutaneously or intramuscularly, may ultimately be responsible for disease complexes of the collagen group as we suspect. As related to the endocrine system, it would seem that Dr. Turner's observations are particularly important since the balance of power between the thyroid, the ovary, the adrenal, and the pituitary gland may be very readily upset by medication during a growth period with harmful and unanticipated results becoming manifest in a later age category. In reference to measuring thyroid function, I would like to ask Dr. Turner to say a word or two. There has been much discussion today about various tests. The newer methods of study may be very accurate in appraising thyroid function especially in a well-integrated medical center, but when it comes to the general practitioner, and the majority do not live in medical centers, I am just wondering how real all of this ideal approach is to him. I wonder if Dr. Turner would give us his opinion of the various tests that are being used, particularly the B.M.R. determination. This test has been degraded today. Maybe it needs to be, but it is still being used widely all over the country, and, in my opinion, if properly performed, yields useful information.

Finally, since we do not yet know how iodine acts in the production of thyroid hormone, I feel that continued studies of this type are to be hoped for.

I have enjoyed Dr. Turner's presentation very much.

Dr. Gretchen V. Squires, Pensacola, Fla. I should like to ask Dr. Turner if, in those cases where the clinician feels that iodine therapy should be continued (in these children), will proper doses of desiccated thyroid balance them into a normal state, or has this been tried?

Dr. Turner (Closing). I should like to reply to Dr. Squires' question first. Some of our patients were permitted to take iodide intermittently while receiving desiccated thyroid but only after the enlarged thyroid had reduced to normal.

It is reported that concomitant maintenance doses of thyroid hormone given along with iodide will prevent interference with normal thyroid function. I doubt the necessity or propriety of prescribing excessive doses of iodides over prolonged periods in any patient. There are other equally effective antiasthmatic agents. I would prefer to use them in patients who demonstrate the iodide blocking effect, rather than trying to overcome it with thyroid hormone.

Dr. Goforth's observations are very pertinent. There are many agents which, though having a specific and desirable effect on disease processes, may also have an adverse action on apparently unrelated organs or systems. This is particularly true of the thyroid.

In addition to an excess of iodides which I have just discussed, thiocyanate, thiocarbamides, and sulfonamides are among a large number of substances which act as goitrogens or interfere with the synthesis of thyroid hormone, or both. As reported by Dr. Booth and Dr. Montgomery this morning, cobaltous chloride has a similar effect.

Dr. Goforth has requested that I give you my opinion of the accuracy of various thyroid function tests, especially the basal metabolic rate.

The various uses of radioactive iodide and the determination of the level of protein-bound iodine in the serum as measures of thyroid activity were very thoroughly presented to us this morning by Dr. Palmer and Dr. Nadler. I believe we agree that the accuracy of these tests is above 90 per cent. However, it is important that the physician be aware of misleading values in these tests and of their source. The administration of iodine in any form, therapeutically or for roentgenologic diagnosis previous to I^{131} tracer studies or the determination of serum PBI levels, will result in a lowered thyroidal uptake and elevated serum PBI.

For example, we have seen recently an elderly woman referred to us for therapy with radioactive iodine. She had a recurrent goiter and was clinically thyrotoxic. The B.M.R. was plus 36 per cent. Tracer studies with I^{131} showed only 5 per cent uptake by the thyroid and urinary excretion of 72 per cent at 24 hours. One week later the level of serum PBI was

11.6 micrograms per cent. A qualitative test for iodine in the urine was strongly positive. We were quite sure the patient was receiving iodine, but she denied any medication except four vitamin tablets daily. Upon investigation these were found to contain 325 mg. of potassium iodide per tablet. The total daily intake of iodide was far in excess of her maximal requirement.

The basal metabolic rate, though considered by some to be only 50 per cent accurate, is still a good test if its vagaries are appreciated. It should be remembered that it is the basal metabolism which is being measured and hypo- or hypermetabolism is not necessarily synonymous with hypo- or hyperthyroidism. Extrathyroid factors such as fear of the test, an uncomfortable bed, insufficient rest, exercise, smoking or eating prior to the test may alter the results.

The basal metabolic rate is usually elevated in pulmonary tuberculosis, heart failure, pregnancy, anxiety states and by a number of drugs.

Fortunately the majority of patients with toxic goiter can be diagnosed by the history, examination and the B.M.R. In doubtful cases and where the newer diagnostic tests are not available the physician may repeat the B.M.R. with the patient under sedation. There will be a definite decrease of oxygen consumption in the neurotic patient but very little in the patient with thyrotoxicosis.

Another simple test is to note the effect of thyroid feeding on the B.M.R. The patient is given 3 grains of desiccated thyroid daily for three weeks. In the thyrotoxic patient symptoms will increase and there will be little, if any, alteration in the B.M.R. If the patient is euthyroid the B.M.R. will decrease 20 per cent or more.

A therapeutic trial of propylthiouracil 300 to 600 mg. daily for 6 to 8 weeks will cause symptomatic improvement and a fall in the B.M.R. Potassium iodide or Lugol's solution will produce the same results, but should not be used as specific therapy nor given if tracer studies or treatment with radioactive iodine is contemplated within 3 to 6 weeks.

Perhaps the most simple diagnostic aid is the sleeping pulse. In the anxiety states the pulse falls to normal during deep sleep, whereas in thyrotoxicosis there is seldom a decrease of over 10 points.

With the above procedures I believe it possible to correctly diagnose most patients with thyrotoxicosis. However, we see an occasional patient who will tax the diagnostic acumen even with all of the laboratory tests available. Fortunately these are few in number.

Results of Treatment with Radioactive Iodine in Heart Disease*

ROBERT PAINE, M.D., *St. Louis, Mo.*

IN SPITE OF THE GREAT ADVANCES in surgery of heart disease and in drug therapy of hypertension, the primary valvular or myocardial disorder cannot be removed in most cardiac patients. For them, therapy is an attempt on the one hand to augment cardiac effectiveness in spite of the basic lesion ,and, on the other, to reduce the demands upon the cardiovascular system. First attempts to reduce the load upon diseased hearts by inducing hypometabolism were made many years ago when total thyroidectomy was done on a few patients. The results did not justify further use of the procedure. However, radioactive iodine has been used more recently with impressive results. In 1,070 patients treated in fifty clinics there was worthwhile improvement in 75 per cent of patients with angina pectoris and in 60 per cent of those with congestive heart failure.[1]

This report is a description of the effects of radioactive iodine therapy in 41 private patients treated during the last four years.

Methods

Patients with angina pectoris or congestive heart failure whose response to conventional measures was inadequate were treated after the determination of the basal metabolic rate, of serum protein-bound iodine concentration, or of radioactive iodine uptake by the thyroid gland. In most cases two or more of these procedures were done. In all cases except one the uptake of a tracer dose of radioactive iodine was measured.

Thereafter a therapeutic dose of 6 to 70 millicuries of radioactive iodine was given in one to three divided doses over a period of

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TABLE 1

Total Cases	41
Total Angina Pectoris	30
Total Congestive Heart Failure	17
Reduction in Angina	27 of 30
Amelioration of Heart Failure	8 of 17
Rheumatic Heart Disease	6
Benefited	4
Hypertensive and/or Arteriosclerotic Heart Disease	35
Benefited	25
Patients Made Worse by R.A.I.	2

one day to three weeks. Most of the earlier patients received 25 millicuries in a single dose. The more recent procedure has been to give three 10 millicurie doses at weekly intervals.

Results

Among the 32 patients with angina pectoris (Table 1) significant reduction, or elimination, of chest pain occurred in 27. Improvement has been reflected in a decrease in the requirement for nitroglycerin and an increase in exercise tolerance. Both exertional and nocturnal attacks have been less frequent or have ceased altogether. A number of individuals who were bed, or chair invalids have resumed their occupations.

Of the 17 cases with congestive heart failure, 8 have improved significantly since radioactive iodine therapy. While the incidence of benefit has been lower in heart failure than in angina pectoris, the degree of improvement in individual cases has been just as striking.

It should be noted that the incidence of improvement does not appear to be related to the primary etiology of the heart disease, for 4 to 6 rheumatic, and 25 of 35 hypertensive and/or arteriosclerotic patients showed beneficial effects.

While the patients having angina reported a sharp reduction in the intake of nitroglycerin, those with congestive heart failure, even those whose improvement was marked, with one exception, failed to show a decrease in the need for digitalis, diuretics or salt restriction. Most patients showed a gain in weight despite an effort to prevent it (Table 2).

Immediately following ingestion of the radioactive material most patients noted no effects. Seven, however, complained of soreness and swelling of the thyroid gland and two patients exhibited signs of hyperthyroidism for a period of days after therapy. They were nervous, sweated freely, were warm, and heart rates were more rapid, probably in response to an abrupt spilling of thyroid hormone into the blood by the irradiated gland (Table 3).

In most instances improvement was not noted in less than one month after therapy, and in some cases a period as long as six months elapsed before evidence of benefit appeared. Improvement usually was insidious in onset and progressed over a period of months. In two patients who had had a decrease in symptoms, a second course of therapy was given one to two years later. In one case the B.M.R. and R.A.I. uptake seemed to indicate that the suppressive effect of the first treatment had been dissipated. Retreatment was again followed by improvement. In the other instance retreatment was given because there had been such progression of the cardiac insufficiency that a further lowering of metab-

TABLE 2

CHANGES FOLLOWING THERAPY

Digitalis Requirement—No change	
Mercurial Requirement—Decrease in 1 patient	
Blood Pressure—No significant effect	
Heart Rate—Decreased 20/min. in 2 patients	
Heart Rhythm—No effect	
Weight— —20 lbs.	
+ 5	
+ 21	
+ 8	
+ 10	
+ 8	
+ 10	
+ 10	

TABLE 3

OTHER EFFECTS OF RADIOACTIVE IODINE

Thyroiditis	7
Hyperthyroidism	2
Hypothyroidism	12
Puffiness of face and hands	
Stiffness of muscles, general aching	
Numbness and tingling of hands and feet	
Coldness	
Sluggishness	
Less prominent—Deafness	
Decreased sweating	
Questionable:	
Intractable nausea (1)	
Gastric ulcers (1)	

olism was required to relieve the patient's symptoms. The second course of iodine was followed by compensation of the failing heart.

As the full effect of thyroid suppression appeared, a remarkably constant syndrome appeared in 12 patients. They first complained of numbness and stiffness of their hands and arms and, within a few days, began to "ache in every muscle." At this time their faces were puffy and pale, and their skin was dry and in some instances more coarse than had been previously noted. Their voices developed a tell-tale brassy hoarseness. Although they complained of sluggishness and coldness, their most insistent complaint was stiffness and numbness of their hands. A decrease in sweating was admitted by most upon direct question. In only one case did a noticeable slight difficulty in hearing occur.

In two instances gastric disorders appeared after ingestion of radioactive material. In one patient, to be described later, intractable nausea began, and in another, some months after therapy, gastric ulcer made itself known by pain and bleeding. It appeared to be benign by x-ray and by therapeutic response.

Examination of the successful and of the unresponsive cases among these 41 persons reveals no relationship between the pretreatment basal metabolic rate and the efficacy of the therapy (Table 4). The basal metabolic rates ranged from plus 28 to minus 15 in those whose symptoms regressed after treatment, and from plus 38 to minus 17 in those who showed no benefit. The average metabolic rates in each group were 4.6 and 5.2 per cent.

On the other hand, a close correlation was

TABLE 4

PRETREATMENT BASAL METABOLIC RATES

Successful Cases		*Failures*
+ 2	— 20	+ 14
+ 13	+ 16	+ 7
— 11	+ 29	— 10
— 15	+ 7	— 17
0	— 1	— 16
0	+ 3	+ 38
+ 28	+ 4	— 5
+ 21	— 5	+ 7
— 7	+ 24	+ 29
— 10	0	
+ 1	— 7	
+ 7	+ 21	
+ 21	+ 20	
+ 2	— 3	

TABLE 5

CHANGE IN BASAL METABOLIC RATE AFTER RADIOACTIVE IODINE THERAPY

Successful Cases	*Failures*
— 15 to — 37	— 10 to — 10
0 to — 8	— 16 to — 7
+ 28 to — 14	— 5 to + 24
+ 21 to + 10	
+ 7 to — 19	
+ 21 to — 7	
+ 2 to — 3	
— 5 to — 23	
— 7 to — 12	
+ 20 to + 7	

observed between responsiveness to therapy and the effect of therapy upon the metabolic rate (Table 5). It is apparent that every successful case in which a pre- and post-treatment B.M.R. was determined there was a decrease in the metabolic rate after therapy. In the few failures in which metabolic rates were recorded before and after radioiodine administration there was no depression of the rate of metabolism.

Protein-bound iodine concentration in the blood prior to therapy was normal in all but one successfully treated patient (Table 6). In the exceptional case the level 3.6 mcg. was slightly below normal limits (4 to 8 mcg.). In only two "resistant" patients were protein-bound iodine determinations made,—one was normal, the other was quite low.

After treatment subnormal protein-bound iodine levels were found in three of four cases. In the fourth case (identified with an asterisk), the ultimate response to therapy had not yet appeared at the time of the PBI determination. Protein-bound iodine was bor-

TABLE 6

PROTEIN-BOUND IODINE LEVEL BEFORE THERAPY

Successful Cases	*Failures*
6.3	2.1
3.6	4.2
4.3	
5.7	
5.1	
8.0	
4.7	

PROTEIN-BOUND IODINE LEVEL AFTER THERAPY

Successful Cases	*Failures*
1.5	
4.2*	3.8
1.6	
2.2	

derline normal in the one unsuccessfully treated patient examined by this method after therapy.

The degree of suppression of metabolism, and not the original metabolic state, is an important factor in determining the success of radioiodine therapy.

This may be most clearly illustrated by the patient whose initial B.M.R. was minus 15 per cent. She was a lady 56 years old who was bedfast with severe angina pectoris of several years duration. Following R.A.I. administration her angina steadily diminished as her B.M.R. fell to minus 37 per cent. At this point she was essentially free of chest pain but was troubled with uncomfortable effects of myxedema. When taking one-half grain of thyroid a day her myxedematous discomforts disappeared but anginal pains began to occur. However, when thyroid intake was reduced to one-quarter grain a day she had neither chest pain nor symptoms of hypothyroidism and she is now an active member of her community. Her experience illustrates the effectiveness of radioiodine in a patient whose B.M.R. was quite low before treatment. Her reaction to thyroid administration also typifies the extreme sensibility of these patients to thyroid extract, one-quarter grain a day being the difference between discomfort and freedom from symptoms.

The essential relation between metabolic suppression and success in therapy can be seen in the case of H. J. This 65 year old man suffered from violent anginal attacks many times each day and consumed enormous quantities of nitroglycerin. Following the ingestion of R.A.I. he failed to improve for four months. During this period the concentration of protein-bound iodine did not decrease. Only after four months did he begin to have the expected relief from angina pectoris.

Patient M.R., on the other hand, noted complete relief from angina within a month. In fact, within two and one-half months he began to have increasingly severe symptoms of hypothyroidism. On thyroid substance, one-quarter, one-half, and finally three-quarter grains a day, the hypothyroid difficulties subsided but anginal pains returned in force. Thyroid dosage was reduced to one-half grain a day and chest pain became much less troublesome, without the reappearance of stiffness, aching and coldness. In this patient a compromise level was not reached at which he could be completely free from both anginal and hypothyroid complaints. It was necessary to accept a situation with an intermediate thyroid intake in which chest pain was rare and mild and no myxedematous symptoms occurred. In many patients with severe cardiac insufficiency this type of compromise was necessary since suppression of body metabolism to a degree sufficient to allow the heart to meet its demands completely produced intolerable myxedema.

This man, 15 months after therapy, developed congestive heart failure which was controlled by usual measures plus a brief omission of thyroid gland substance. The progressive enlargement of his heart and the occurrence of heart failure testify to the progression of his heart disease in spite of the induced hypothyroidism. This and many other cases demonstrate the fact that radioiodine therapy has little, if any effect upon the progression of the primary cardiac disorder. Rather, it is a symptomatic, palliative agent that accommodates the recipient to his circulatory defect.

Another patient in whom chest pain was eliminated as stiffness and muscular aching appeared was a 63 year old man with aortic stenosis, Stokes-Adams attacks and angina pectoris. His pretreatment B.M.R. was plus 20 per cent, although his radioiodine uptake by his thyroid gland was normal (29 per cent). It may be that his hypermetabolism was an example of the nonthyroid elevation of metabolic rate seen in some cases of aortic stenosis. This is further suggested by the finding of a plus 7 per cent B.M.R. at the depth of his typical myxedematous symptoms seven months after therapy.

Between the seventh and tenth months after treatment he quite spontaneously became less and less hypothyroid in appearance and in symptoms, and his chest pain became increasingly prominent. Finally, 10 months after treatment, his B.M.R. was again plus 20 per cent and all evidence of his radioiodine effect had melted away. Thereupon, a second course of iodine was given and again anginal pains ceased and hypothyroid symptoms began to occur. This time, however, thyroid was given in sufficient dosage to eliminate almost all stiffness, swelling and aching without precipitating recurrence of angina. Once

again it should be noted that the fundamental process appears to have gone on, leading finally to the sudden type of demise with which aortic stenosis is often associated.

Another example of the progression of heart disease in spite of iodine therapy is seen in A. B., a 55 year old man who noted convincing improvement for some months after a second course of radioiodine. He then began to have troublesome symptoms of hypothyroidism. When thyroid substance was given in amounts as small as one-tenth grain, to as large as one and one-half grain a day he noted a prompt increase in angina and abandoned thyroid therapy. It would appear that his coronary insufficiency had progressed to such severity that even a myxedematous state was productive of chest pain.

Success in the relief of anginal symptoms was marred in O. H. by the simultaneous development of intractable nausea in association with aching and edema. This 67 year old woman had had talcum powder placed in the pericardial sac with satisfactory control of chest pain, only to be involved in an auto accident and receive an anterior chest injury which was followed by the recurrence of violent angina pectoris. She was severely hypertensive and had had abdominal and gastrointestinal complaints since childhood. No cause was found for her nausea. Its relation to radioiodine was difficult to establish in view of the long history of gastric complaints. Thyroid substance appeared to relieve the more typical myxedematous symptoms but did not influence the nausea.

The effects of hypothyroidism may, on occasion, lead to confusion in the interpretation of symptoms. On two occasions in a 62 year old man with angina pectoris, development of increasing facial and leg edema and gain in weight at first appeared to be due to hypothyroidism. Subsequent occurrence of dyspnea and response of all symptoms to digitalis indicated their myocardial origin.

An episode of increasing pallor, swelling and anginal pain led to confusion in the handling of this patient until evidence of gastrointestinal bleeding and anemia was discovered to explain the paradoxical simultaneous occurrence of what appeared to be deepening hypothyroidism and increasing angina.

Among the patients who had failed to benefit from radioactive iodine therapy, some appear to have failed because there was no suppression of thyroid function. Five patients died ten days to two months after therapy and enough time may not have elapsed to permit hypothyroidism to develop. One unsuccessfully treated patient was found to have protein-bound iodine concentration at the lower limits of normal (3.8 mcg.) 19 months later. No explanation for the failure to suppress thyroid function was discovered.

In three patients, one with rheumatic heart disease and two with hypertensive and arteriosclerotic heart disease, no benefit was noted despite the development of definite hypothyroidism. It is felt that these were patients whose cardiac performance was not adequate to meet even the reduced needs of hypometabolic tissues.

In two instances it appeared that the transient period of hyperthyroidism immediately following ingestion of the iodine may have played a role in the downward course of the patient. One man, aged 60, who had severe arteriosclerotic heart disease with angina and a history of myocardial infarction, became increasingly apprehensive, warm, and sweaty after therapy, and showed progressive evidence of myocardial failure, dying on the tenth day after therapy. The other patient, a 67 year old man with progressive heart failure, a B.M.R. of plus 38 per cent, PBI of 4.2 mcg. and uptake by the thyroid gland of 52 per cent of a tracer dose of radioiodine continued to fail rapidly and died two months after treatment.

These two cases illustrate the folly of treating rapidly deteriorating patients in whom there is both the danger of a significant cardiovascular burden during the period of hyperthyroid reaction and also the likelihood that the patient cannot survive long enough to benefit from induced hypothyroidism. It is this hazard of an excessive discharge of thyroid hormone that justifies the division of radioiodine dosage into three weekly fractions.

The beneficial effects of this agent have, at times, been most remarkable. A 21 year old woman, having rheumatic heart disease, was treated in December of 1954. At the time of therapy she was unable to leave her bed because of dyspnea. Her abdomen was distended with fluid and her liver was painfully con-

gested. She had had attacks of pulmonary edema. On conventional hospital treatment for many weeks she made little or no progress. Her course since radioiodine has been a steady improvement from invalidism. She is now an active housewife who takes full charge of her home and participates in community functions and sees her doctor at monthly intervals. There are no edema, ascites, nor abdominal pain, and no dyspnea in the ordinary routine activities. This compensation has occurred without the development of symptomatic hypothyroidism.

Another patient with rheumatic heart disease has displayed effects sufficiently remarkable to be worthy of description. She is a 42 year old woman with aortic and mitral valvular disease who presented severe congestive heart failure and mild angina pectoris. Prior to treatment her B.M.R. was plus 20 per cent and PBI was 6.3 mcg. She made a prompt response to iodine therapy, becoming free of congestive and anginal symptoms by the third month. Some ten months after treatment, however, her symptoms recurred and reached such proportions that it was feared that she was in the terminal days of heart failure. At this time, despite evidence of hypothyroidism on physical examination and on determination of the PBI (1.5 mcg.) she was given a second course of radioiodine. Her symptoms have once again been dissipated to a large extent. Apparently it has been possible to reduce the demands upon her cardiovascular system sufficiently by the second course of therapy, in spite of the hypothyroid state that existed prior to the administration of the iodine, to give her relief. While the PBI was 1.5 mcg. and her appearance was distinctly hypothyroid, the B.M.R. in this patient was plus 10 per cent and uptake of tracer iodine by her thyroid gland was normal, 30 per cent. This is one of many examples of discrepancy in these cases between B.M.R., PBI, and tracer dose uptake (Table 7).

TABLE 7

COMPARISON OF			
BMR	*PBI*	*Per Cent R.A.I. Uptake*	
11		40	
7		16	
—15		30	
—10		31	
28		15	
21	6.3		
— 7		14	
— 6	3.6	42	
1		36	
7		30	
21	4.3	36	
—17		26	
—16		20	
2		21	
38	4.2	52	
—20	4.7	40	
16		45	
29		60	
	5.7	47	
7		22	
1		31	
3		39	
— 5		32	
0		21	
7		34	
29		41	
— 7		31	
21		25	

While much of this discussion has been concerned with the failures and difficulties in radioiodine therapy of heart disease, it would be improper to conclude that the use of the agent is so fraught with difficulties as to be of questionable value. As indicated in table 1, 27 of 32 patients with chest pain and 8 of 17 with heart failure were significantly relieved of their cardiac symptoms. Of the 41 patients, 26 were improved without the production of hypothyroid symptoms of such severity as to detract from the over-all result.

Conclusions

1. Radioactive iodine therapy is an effective palliative agent in the treatment of heart failure and angina pectoris.

2. It is more frequently effective in angina pectoris than in cardiac decompensation.

3. The ultimate usefulness cannot be predicted from the basal metabolic rate prior to therapy.

4. No benefit is obtained unless there is a significant suppression of metabolism.

5. The incidence of success is the same for rheumatic, hypertensive and arteriosclerotic patients.

6. Failures occurred in patients whose metabolism was not suppressed, in patients whose cardiac insufficiency could not be erased even by hypometabolism, and in patients who did not survive long enough to become hypothyroid.

7. Radioiodine is most effective in patients whose disease is stable and not rapidly progressive. Indeed, the agent may be danger-

ous if used in the presence of rapidly deteriorating heart disease.

8. Classic symptoms of hypothyroidism may be produced but are usually controlled by one-tenth to three-fourths of a grain of thyroid a day.

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Discussion (Abstract)

Dr. Philip C. Johnson, Oklahoma City, Okla. Pericardial surgery, nerve block and thyroidectomy all have resulted in significant improvement in many of these chronically ill patients. However, none of the technics has been compared by the same individual in his own practice, and to my knowledge none of these reports has utilized a control group. Dr. Blumgart has attempted to control his series by insisting upon treating only those patients whose symptoms were both stable and chronic for a considerable length of time prior to radioactive therapy.

While Dr. Paine did not mention it in his excellent paper, I presume that he follows Dr. Blumgart's criteria. Thyroidectomy for intractable angina and congestive failure goes back to Dr. Blumgart's early work in which he showed that cardiac work is decreased in frank myxedema. Radiation thyroidectomy presents a simple and potentially permanent way to produce myxedema. In the euthyroid individual, doses of 30 to 100 millicuries are required for a clinical effect. Any thyroid response below this suggests that in reality we are dealing with a thyrotoxic patient, perhaps with a masked thyrotoxicosis. This therapy attempts to produce a nebulous clinical state which is neither euthyroidism nor myxedema but in which the patient is less symptomatic. Sixty to seventy-five per cent of patients show some symptomatic improvement after this therapy.

Over the past six months, I have had the fortune to see four patients with chronic angina and/or chronic congested failure who were myxedematous. All became essentially asymptomatic with proper thyroid medication. Myxedema should be looked for as a complication of already existing heart disease in anyone who has ever been treated with radioactive iodine. As thyroid function decreases, the serum cholesterol rises, usually above 300 milligrams per cent. What effect this might have on the ultimate longevity of these cardiac patients can only be conjecture.

Dr. J. R. Maxfield, Jr., Dallas, Tex. I think this paper is very significant. It brings out something that all of us must stop a moment to think about. When a new technic is introduced, it usually goes on a trial basis with many theoretical disadvantages suggested. This has been the case with radioactive iodine used in this manner. This, however, is a technic that is certainly completely reversible at any time by the addition of thyroid extract and, therefore, can be considered completely safe. The premise that this treatment should be used only on people who have had exhaustive attempts at control with repeated failures or persistent angina over a long period of time, is delaying the procedure too long.

I think this treatment should be instituted relatively early in the control of patients with angina or cardiac failure in conjunction with the other methods of treatment which are used by the specialists in internal medicine. By doing this the control of the patient can be accomplished with dosages, probably a little smaller, over a more protracted period of time than has been reported here. This could certainly have no effect that would be deleterious to the patient. To say that this technic should be withheld until the patient has had all other trials of treatment and is getting into more difficulty, is like waiting to throw the life preserver to the fellow when he is getting ready to go down the third time. I believe that the life preserver should be sent out to him the first time he goes down. Let us recommend this radioiodine treatment early, when it is most effective.

Dr. Henry H. Turner, Oklahoma City, Okla. I wish to report that our experience in the occurrence of thyroid storm or crisis following therapy with radioactive iodine has been much less tragic than that of Dr. Paine. In our series of almost 700 patients who have been treated with I^{131} during the past 5 years, we have had 2 patients who developed post-therapy crisis: one, a man aged 59 years in whom symptoms appeared within 12 hours after a therapeutic dose of 3 millicuries; the other, a woman aged 46 years, a severe thyrocardiac, who became comatose within 18 hours after taking 4.7 millicuries of I^{131}. Both patients recovered.

It is my opinion that in either instance, crisis was impending and that it was not precipitated by the isotope inasmuch as radiation effects within this short period of time are almost nil and certainly are not sufficiently intense to cause an appreciable increase in production of thyroid hormone.

I recently sent a questionnaire to 15 of the pioneer users of radioactive iodine with reference to the occurrence of thyroid storm, following I^{131} therapy in their patients. They reported 5 cases of storm in approximately 10,000 patients treated.

It appears that though the condition is rare, it does occur in some following I^{131} therapy and more often in the severe thyrocardiac as Dr. Paine has reported.

Dr. Paine (Closing). I appreciate these comments very much.

I do not mean these two patients, Dr. Turner, that I referred to were necessarily in storm, as we would call it. These individuals had such a borderline reserve, that the meager beginnings of storm were enough to push them along the downhill way. Both individuals did have sore glands that were enlarged, their pulses did accelerate, and they did sweat more. I do not have the information as to whether their PBI's went up or not, which, of course, would help unsettle them.

I agree that this agent is very effective, but I think it is one that is not completely safe although it may be used at any early time in an individual with com-

plete safety. The dangerous patient is the one who has no reserve left. I think it is safe to use it even there, if the patient is not deteriorating before your eyes. The ones that I have had trouble with are the ones who were rapidly deteriorating as I treated them. Those people, I think, I have hurt in two instances. As time has gone on, I have tended to treat patients earlier than I did at the beginning. I have used the divided dosage, and in the last half of this series, I think there has been little harmful effect that could be substantiated.

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Segmental Saphenous Ligation in the Ambulant Versus Stripping of Varicose Veins*

WILLARD BARTLETT, M.D.,† *St. Louis, Mo.*

The author considers carefully the anatomic and physiologic aspects of varicose veins. He then compares the methods of dealing with this abnormality.

IT IS MY PURPOSE to review the anatomic and functional defects which must be corrected if one is to cure primary varicosities of the saphenous veins, to comment on the methods used for their detection, and to examine the evidence for the claim that stripping of the saphenous trunks is more effective than a multiple ligation technic alone. A comparison will be offered between the respective degrees of discomfort, periods of disability and hospital expense involved in the two procedures. The writer is not an unbiased witness and professes a continuing, strong preference for the performance of multiple ligations on an ambulatory basis as the procedure of choice in the great majority of patients with primary varicosities of the saphenous vein. This paper will not consider the treatment of varicose ulcer nor the consequences of thrombophlebitis of the deep veins of the lower extremity and pelvis.

Anatomy

Fossa Ovalis. Important information as to the veins in and about the fossa ovalis has come from the dissections of cadavers and surgical patients by Sherman[1] (137 cadavers, 465 patients) and Daseler and associates[2] (350 consecutive dissections). Of the tributaries entering the long saphenous trunk within 6 cm. of the saphenofemoral junction, 96 per cent had their junction in the proximal 3.5 cm. Daseler and others have emphasized the finding that tributaries of deep muscle veins frequently enter the trunk within the fossa ovalis and these should be divided, however small they be, during the performance of high ligation.

I have seen within the past year a vein of 3 mm. diameter join the medial aspect of the saphenous trunk only 1 cm. distal to the saphenofemoral junction; it coursed distally below the deep layer of the fascia lata in a plane superficial to the superficial femoral vein. If the cribriform fascia had not been adequately opened and the saphenofemoral junction fully exposed, this tributary would have gone unseen in the course of a more superficial dissection such as division of the saphenous trunk at the level at which it penetrates the cribriform fascia. I do not recall having previously seen a description of this subfascial, saphenous tributary vein; it joined the long saphenous trunk at a point much higher than does the high Hunter canal "E" vein described by Sherman as a rarely found, direct communication at a point 6 to 8 cm. distal to the saphenofemoral junction.

In dividing the cribriform fascia and opening the fossa ovalis for full visualization of the saphenofemoral junction, it is worth recalling an anatomic detail of importance described by Daseler and his associates. The femoral artery lies partly concealed under the lateral (falciform) margin of the fossa; it was found more or less completely exposed in the fossa in over 75 per cent of 200 consecutive dissections. While it seems incredible, there is at least one published report of unwitting ligation of the femoral artery which was mistaken in recent years for the long saphenous vein.

Venous Valves. Perhaps the earliest study

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of the development of the venous valves is that of Kampmeier and Birch[3] on human fetuses and cadavers. These authors described 6 to 14 valves in the long saphenous trunk, excluding the foot. Bicuspid valves constitute the vast majority and tricuspids form the most common deviation. Of the six locations in the long and short saphenous systems at which valves are found, the most constant are within one inch of the saphenofemoral and saphenopopliteal junctions (usually at the inosculation) and immediately distal to the entrance of a tributary, the latter often entering directly into the sinus, where the wall of the vein is thinnest. The outlets of the tributaries, however small, have valves as often as not. The first anlage of the valves appears at three and one-half months in the fetus and the full quota is probably established by the end of five months.

Among the interesting reflections by the authors is their opposition to the assumption that the valves diminish the influence of gravity or weight of the column of blood which would require one to believe that the blood "stands still" with the body in the erect posture and that the valves are then closed. These authors contend that the normal flow of blood requires the sinuses to be collapsed and the valves open except momentarily, regardless of posture, and that the prevalence of valves in the extremities (as elsewhere about such muscular organs as the stomach) serves to prevent regurgitation during muscular exertion. It is hard to differ with these views.

Superficial Veins of the Thigh and Leg. There is too prevalent a concept among clinicians that the superficial venous return from the lower extremity is rather sharply divided between the long and short saphenous systems with the main trunks as the most important components. In the presence of venous disease, particularly, a more useful approach puts the emphasis on the secondary and primary tributaries of both systems which anastomose freely among themselves, with one another, with the subfascial veins of muscles and deep venous trunks, and with superficial tributaries of certain extrasaphenous venous systems, notably the parietal tributaries of the pelvic veins. From such a viewpoint the long and short saphenous trunks themselves are seen as the most prominent, but by no means the exclusive routes by which superficial venous blood leaves the lower extremity.

Sherman[1] has reported extensive dissections of the long and short saphenous veins in the thigh. He shows that the long saphenous trunk pierces the superficial layer of the deep fascia in its distal course in the upper thigh whereas the accessory saphenous (which is the fetal pattern), when present, stays superficial to this layer. Frequent duplication of the long saphenous trunk is described and communication with the short saphenous through tributaries, particularly the superficial medial circumflex femoral, on the medial and posterior aspect is common.

Perforator Veins of the Thigh and Leg. Mathiesen[4] states that the significance of incompetence of the perforating veins which pierce the deep (crural) fascia of the thigh and leg to provide anastomosis between the superficial and deep venous systems of the lower extremity was recognized prior to 1910 by many European authors, notably the German. Their importance was lost sight of for many years and interest in their existence and their role in the development of venous stasis was re-awakened only in 1936 and thereafter. Dissatisfied with the failure of either high saphenous ligation or local sclerosing injections to relieve distal varices, Mahorner and Ochsner[5] devised the comparative tourniquet test in the expectation of isolating incompetent communicating veins of the thigh below the saphenofemoral junction.

The paper by Linton,[6] in 1938, contributed importantly to our knowledge, since his report detailed the findings in dissection of 10 injected legs and 50 operations for incompetent perforator veins. Normally these veins are thin-walled and no larger than 2 mm. in diameter. Diseased, they may reach 5 mm. in size. Linton groups them as connecting the long and short saphenous veins with their principal deep destinations and topographical location thus: (1) to posterior tibial, along medial aspect, from long saphenous; (2) to anterior tibial, on anteromedial, anterolateral and anterior surfaces, from both long and short saphenous; (3) to peroneal, on posterolateral surface, from short saphenous; (4) inconstanly to popliteal,

usually piercing the deep fascia on the posterior below the middle third. The frequency is given as medial, 80 to 90 per cent, lateral, 15 per cent, anterior, 5 per cent. Linton's findings are not confined to patients with primary varicosities. In advocating subfascial ligation of incompetent perforators through long, vertical incisions, he comments that their interruption had been recommended by Rémy in 1901, by Homans in 1916 and by Trout in 1929.

The publications by Sherman[1,7] reporting (1944) thigh dissections on 73 cadavers and 746 patients, and (1949) leg dissections on 63 cadavers and 482 patients are of monumental proportions. On the whole, his findings in the leg confirm those of Linton but with important additions. He is the first to describe accessory perforator veins ("Q" veins) which may pierce the fascia at still other sites. He also demonstrates that perforators most frequently anastomose superficially with secondary or primary tributaries of the saphenous systems or with veins connecting those systems.

In the leg, the greatest frequency with which incompetence of perforators appears in his surgical patients is as follows: medially, perforators number 2, 35 per cent; number 3, 20 per cent; number 1, 17 per cent (at or below midleg connecting with posterior tibial); posterolateral, 25 per cent, to peroneal; saphenofemoral junction, 15 per cent; calf, connecting principally secondary tributaries of long and short saphenous to veins of the calf muscles, 12 per cent. Of all the perforating veins in the five groups of Sherman, only the medial perforators 3, 4 and 5 (at or above midleg adjacent to the margin of the tibia) have their principal connections *directly* from the long saphenous trunk to a deep vein, in this case the posterior tibial. Even these perforators have also accessory ("Q") veins that make only indirect connections through saphenous tributaries.

Practically all of the perforator veins found in the thigh by Sherman were on the medial aspect and at two levels, the junction of the upper and middle thirds and the upper border of the patella. Those at the higher level arise from the constant mid-Hunter canal vein, the lower from the genicular plexus; at either level the long saphenous trunk or its tributaries may also receive a perforator from the subsartorial vein which frequently connects the mid-Hunter canal vein and the genicular plexus. These anastomoses with the perforators of the thigh are as often indirect as direct with the main superficial trunk. In 101 dissections, the largest number demonstrated was 6, the smallest one. In operations on the thigh, incompetence of the mid-Hunter canal perforator was found in 6.7 per cent, of the genicular perforator in 1.6 per cent, and of lateral perforators in 1.3 per cent. The valve at the saphenofemoral junction was incompetent in 100 per cent of cases.

Sherman's publications do not allude directly to the classifications of varices among his operative cases as being either primary or secondary. In the 1949 report on incompetent communicators operated on after 1944 is the note that in addition to 157 patients examined one year after operation, 19 were excluded from the report because of the presence of vulvar varicosities along with 9 cases of preoperative thrombophlebitic sequelae, nearly 19 per cent of the total. Comment will be made later on his operative technic and reported results.

In summary of the anatomic and clinical studies set forth above, we must face these fundamental facts:

1. In primary varicose veins of the lower extremity, recognition and interruption of valvular incompetence in perforator veins is a frequent requirement and its operative relief is as important as for saphenofemoral or saphenopopliteal incompetence.

2. Valvular incompetence of perforator veins is far more common in the leg than in the thigh.

3. The majority of anastomoses between perforator veins and the saphenous systems are made with tributaries, primary or secondary, of the latter rather than with the main trunks.

4. The sites at which incompetent perforators pierce the deep fascia do not usually coincide with the point of maximum dilatation of the superficial veins.

Methods of Examination

The shortcomings of tests employing a tourniquet at a level distal to the fossa ovalis are slowly gaining recognition. I have

not placed any confidence in them since 1946 and do not use them in making the diagnosis of valvular incompetence nor as an accessory to the localization of sites of incompetence. Tributaries of the saphenous trunks usually take a course which has a vertical, as well as a transverse component; the same is true of connections between the long and short saphenous systems. Circumferential pressure may occlude tributary vessels carrying blood from areas of valvular incompetence either medial or lateral to the axis of the trunk which usually occupies the examiner's attention. Confusion is introduced by the application of a tourniquet if more than one incompetent vein traverses the same plane but on different aspects of the extremity. Others who have abandoned the use of the tourniquet tests as misleading, or who have recorded their mental reservations as to their value are Pratt,[8] Steiner and Palmer,[9] Massell and Ettinger,[10] Sherman,[1,7] Prioleau,[11] and Luke.[12] Among the few authors who continue to regard multiple tourniquet tests highly is Barrow[13] who, in 1951, reiterated his belief in its value as expressed in his monograph.[14] Massell and Ettinger[10] could confirm at operation only 54 per cent of perforator veins localized by tourniquet tests as being incompetent; 86 per cent confirmation of incompetent perforators localized by phlebograms was obtained.

I have a high regard for Pratt's[8] method of localization of incompetent perforators by the use of elastic bandages. In conjunction with its use, I have developed a method of systematically palpating the visible or palpable tributaries above any segment of the popliteal trunk in which retrograde flow can be shown to be present by digital compression. A point is reached in the tributaries beyond which compression will no longer prevent distention of the larger tributaries and trunk; this is the site at which the incompetent perforator pierces the fascia and is amenable to direct attack. This method, believed to be original, is tedious but rewarding in its accuracy. I share the frequently expressed view of one of my former teachers, F. A. Coller, that the time best worth saving is that from the institution of treatment to full recovery.

The Choice of Operative Procedures

My disapproval of routinely stripping the saphenous trunks has already been made clear. As a house officer in the University Hospital, Ann Arbor, I saw the abandonment of the use of the extraluminal stripper, not because it was tedious, but because it was relatively ineffective in preventing persistence of varices. From the anatomic evidence as to the remoteness of the site of passage through the fascia of many perforator veins, it has always seemed obvious that tearing loose the trunks from the primary tributaries and such perforators as enter the trunks directly could not deal adequately with the situation. Granting perfectly performed ligations at the saphenofemoral and saphenopopliteal junctions, as indicated, individual division of the incompetent perforators at or beneath the fascia fulfills the requirements for cure of primary varicosities as stripping does not. On the basis of a limited experience, I will extend that assertion to the treatment of the varicosities of patients with only mild residuals of deep thrombophlebitis, other measures being directed at the deep venous trunks and the superficial fibrosis and ulcers.

Others who do not practice stripping or assign it only limited value are McElwee and Maisel,[15] Slevin,[16] Massell and Ettinger,[10] Sherman,[7] Stalker,[17] Prioleau[11] and Mathiesen.[4] I have found no published series of operative results by advocates of stripping which will stand scrutiny as to percentage of patients operated upon coming to follow-up, adequate length of follow-up or appraisal of results, although publications meeting these criteria may appear in the future. Of six articles advocating stripping in several leading surgical journals during the past 5 years, only two offered any data as to results. The best comparison to date of the respective results of multiple ligation and of high ligation plus stripping is that of McElwee and Maisel.[15] Somewhat better results were seen in one year following multiple ligations though the stripping itself was not usually extended into the leg. Excision of the long saphenous trunk through segmental incisions is practiced by Sherman,[7] Massell and Ettinger[10] and Prioleau.[11]

Disability and Expense

I was recently furnished with the following data on all patients hospitalized by Blue Cross in eleven St. Louis hospitals during the five months from May to September, inclusive, 1955, for stripping of varicose veins. For the 231 cases there was an average length of stay of 8.1 days. The average hospital bill was $128.00; this excludes fees for anesthetic, x-ray and laboratory tests other than "routine" (these are paid only by Blue Shield in Missouri).

This hospitalization expense, necessitated by the performance of stripping under general anesthesia, is in marked contrast with the hospital costs entailed by ambulatory ligation performed under local anesthetic. These add up to $41.50, divided as follows: operating room use $25.00 if the procedure continues into the second hour, $2.50 for anesthetic solution, 2 elastic bandages at $2.00 apiece. (Since I frequently operate on only one leg at a sitting, this cost will be doubled to patients having bilateral operations at two stages.) Bilateral operation at one stage increases the cost by not more than $10.00.

According to my colleagues who habitually do only stripping operations, an estimate of two weeks of disability from a reasonably active occupation is conservative. There is ordinarily no disability from gainful occupations or the performance of housework after multiple ligation except on the day of operation. I had such an operation performed upon myself in 1953, and returned to my customary duties on the following day.

Summary

1. The anatomic data of recent years indicate that such perforator veins as may have valvular incompetence in primary varicose veins are more effectively dealt with by individual ligation than by stripping of the saphenous trunks.

2. I am unable to find any published evidence to warrant the view that stripping of the saphenous trunks has given results superior to those achieved by multiple ligations.

3. There is a growing belief, supported by anatomic findings, phlebograms and operative inspection that the application of tourniquets distal to the fossa ovalis is more misleading than helpful in the diagnosis and localization of valvular incompetence in perforator veins.

4. A method of progressive digital occlusion of the saphenous tributaries, the saphenofemoral junction being simultaneously compressed, is described as a reliable means for the diagnosis and localization of perforator incompetence.

5. The hospital costs averaged $128.00, exclusive of general anesthetic fees, for 231 consecutive cases hospitalized for vein stripping. The hospital costs incurred in ambulatory, multiple ligation do not exceed $50.00 for one stage, bilateral operation, less than a third as great as for stripping.

6. Disability from many gainful occupations is not less than two weeks after stripping. Disability of more than one day is uncommon after multiple ligation.

7. In my opinion, stripping of saphenous trunks is a useful addition to other operative procedures only in the presence of very gross dilatation of the trunks and of primary tributaries. In this situation, there is usually fibrosis of the veins with incompetence of the valves of numerous primary tributaries. Such dilated segments do not completely collapse when the extremity is elevated; after ligation alone, these veins fill from below to such an extent that they remain unsightly and require, at times, extensive postoperative injection for their obliteration. The amount of sclerosing treatment to be done in advanced cases will be sharply reduced by operative stripping of main trunks and of such fibrotic collaterals as can also be removed thus. If these criteria for stripping are observed, the incidence of justifiable stripping in the practice of any given surgeon may vary widely from that of a colleague. The difference in practices then is due to the differences in the problem to be solved, not to blind adherence to one doctrine or another without individualizing the need of the patient.

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An Evaluation of Antiemetic Agents in the Control of Vomiting in Children*

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Because of the resultant dehydration from vomiting in children, its control is desirable. Some of the newer tranquilizing drugs offer an answer to the problem in certain causes of vomiting.

THE SYMPTOMATIC CONTROL OF VOMITING is frequently a valuable therapeutic adjunct in the management of sick children. No more rapid and pernicious source of dehydration occurs more commonly than severe unrelieved emesis. Vomiting in children is often a secondary symptom in acute febrile illnesses, e.g., tonsillitis, otitis media, etc., where the severity of the emesis may be such as to make impractical any oral antimicrobial therapy. In addition, no matter how skilled the physician may be in the area of water and salt metabolism, most authorities agree that rehydration of dehydrated subjects can be carried out with greater safety and efficiency by the oral rather than the parenteral route if vomiting is not present.

In recent years several new drugs have become available which appear to be both safe and effective antiemetic agents. General interest in these drugs stems from the above considerations. This report is based upon our clinical experience in children with three of these antiemetic agents: chlorpromazine (Thorazine-Smith, Kline & French), Meclizine (Bonamine-Pfizer), and Cyclizine (Marezine-Burroughs Wellcome).

Material and Methods

Over a two and one-half year period, 252 patients with vomiting in association with a wide variety of illnesses have been treated by the pediatric staff of the Jefferson Davis City-County Hospital. Only patients whose vomiting appeared to be severe were selected for this study. The age of the patients ranged from 1 month to 14 years with a predominance of patients in the under 5 year age group. In so far as possible other medications were not given, or were withheld until the response to the antiemetic agent could be established. Parents were urged to continue the patient on a full diet and particularly to urge fluids. A grading system was established to classify the results obtained and this same system was used throughout. A group of cases previously described in a preliminary report[1] are also included here and have been regraded by this system.

The criteria established for evaluation are as follow:

Excellent. The response to antiemetic therapy was considered excellent if severe and protracted emesis was completely controlled and a normal diet was taken.

Good. A grade of "good" was assigned to those patients in whom vomiting was controlled and hydration maintained even though some anorexia and nausea persisted.

Equivocal. The influence of antiemetic therapy on the course of vomting was difficult to evaluate in some cases either because a limited diet was offered the patient or because the medication was improperly prescribed.

Poor. This grade was assigned to all cases not fulfilling the requirements for one of the first three categories.

For simplicity the grades of "excellent" and "good" have been combined in the data tables

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TABLE 1

DOSAGE SCHEDULES FOR ANTIEMETIC THERAPY

Drug	*Route*	*mg./Kg./dose*	*Frequency*
Chlorpromazine	I.M.	0.5	every 4-6 hrs.
	Oral	1.0	every 4 hrs.
	Rectal	2-3	every 4 hrs.
Meclizine	Oral	2-3	every 4-6 hrs.
Cyclizine	Oral	1-2	every 4-6 hrs.
	Rectal	3-5	every 4-6 hrs.
Secobarbital	Rectal	2-4	every 4 hrs.
Placebo	Rectal		

since both represent a satisfactory response to medication. The dose of medication has been determined in previous studies and in general is that quantity of medication that will control vomiting without excessive side effects (Table 1). This dose varies with the route of drug administration, the intramuscular or subcutaneous route being the most effective.

Results

Table 2 illustrates the over-all results of therapy. As is readily apparent our greatest experience has been with chlorpromazine. This fact makes any estimate of relative efficacy invalid; however, all three antiemetic agents were strikingly effective. The good responses in the placebo group illustrate the difficulty of evaluating any agent in the symptomatic management of an unpredictable condition such as vomiting. Nevertheless, the patients treated with Secobarbital and a placebo had a much poorer response than did the patients given an antiemetic agent.

If the data for individual drugs are examined in relation to the etiologic type of vomiting (Table 3) it will be seen that in the group treated with chlorpromazine acute gastroenteritis is the most common diagnosis but that failure of therapy occurred most commonly in vomiting associated with cough and bronchitis, bulbar poliomyelitis, and pyloric stenosis.

Lack of success in patients whose vomiting was primarily associated with severe cough is not unexpected, nor was the failure of chlorpromazine to control vomiting in pyloric stenosis surprising. If the patients in whom no evaluation could be made (i.e., the equivocal group) are excluded it will be seen that the vomiting in 134 of 145 patients, or 92 per cent of the patients treated with chlorpromazine was satisfactorily controlled, as opposed to 8 per cent in which the response to

TABLE 2

SUMMARY OF GROSS RESULTS OF ANTIEMETIC BARBITURATE AND PLACEBO THERAPY

Drugs	*Number Patients*	*Response* *Good*	*Poor*	*Equivocal*
Chlorpromazine	155	134	11	10
Meclizine	31	24	3	4
Secobarbital	20	12	7	1
Cyclizine	17	16	1	0
Placebo	29	19	8	2
Total	252			

TABLE 3

SUMMARY OF THE PRIMARY DISEASE AND CLINICAL RESPONSE TO ANTIEMETIC THERAPY WITH CHLORPROMAZINE IN 155 CHILDREN

Diagnosis	*Number Patients*	*Response* *Good*	*Poor*	*Equivocal*
Acute gastroenteritis	90	82	2	6
Functional vomiting of infancy	6	5	0	1
Acute bronchitis, pertussis or laryngo-tracheo-bronchitis	8	4	3	1
Upper respiratory infection (coryza, otitis media, tonsillitis)	17	16	0	1
Diabetes with acidosis	3	3	0	0
Poliomyelitis, bulbar	3	1	2	0
Psychogenic vomiting	6	6	0	0
Chemical gastritis (aspirin, antibiotics, hydrocarbons, etc.)	4	3	0	1
Meningitis and encephalitis	3	2	1	0
Malignancy	6	5	1	0
Pyloric stenosis	2	0	2	0
Miscellaneous	7	7	0	0
Total	155	134	11	10

TABLE 4

SUMMARY OF THE PRIMARY DISEASE AND CLINICAL RESPONSE IN PATIENTS TREATED FOR VOMITING WITH MECLIZINE AND CYCLIZINE

Diagnosis	*Number Patients*	*Response* *Good*	*Poor*	*Equivoca*
Meclizine				
Acute gastroenteritis	16	13	1	2
Upper respiratory infection (coryza, tonsillitis, otitis media)	10	8	1	1
Meningitis	2	1	0	1
Miscellaneous	3	2	1	0
Total	31	24	3	4
Cyclizine				
Acute gastroenteritis	4	4	0	0
Upper respiratory infection (coryza, tonsillitis, otitis media)	7	7	0	0
Meningitis	2	2		0
Miscellaneous	4	3	1	0
Total	17	16	1	0

TABLE 5

SUMMARY OF THE PRIMARY DISEASE AND CLINICAL RESPONSE OF PATIENTS TREATED FOR VOMITING WITH SECOBARBITAL AND PLACEBO

Diagnosis	Number Patients	Response Good	Poor	Equivocal
Secobarbital				
Acute gastroenteritis	12	7	4	1
Upper respiratory infection (coryza, tonsillitis, otitis media)	6	4	2	0
Miscellaneous	2	1	1	0
Total	20	12	7	1
Placebo				
Acute gastroenteritis	10	6	4	1
Bronchitis	4	2	1	1
Upper respiratory infection (coryza, tonsillitis, otitis media)	8	7	2	0
Central nervous system disease	3	2	1	0
Miscellaneous	2	2	0	0
Total	29	19	8	2

therapy was considered poor. Examination of our limited experience with Meclizine and Cyclizine (Table 4) reveals comparable results. Here again two out of four of the failures were in patients who vomited in association with a severe cough.

Forty-nine patients (Table 5) were treated with a barbiturate sedative or placebo. The response in these patients is of interest for it measures to some extent the influence of sedation, and provides an estimate of the relative incidence of self-limited vomiting in this series. These patients are part of a special study and will be commented upon later in the text in more detail.

Side effects (Table 6) of antiemetic therapy were largely limited to drowsiness. Although every effort was made to record any side effects during therapy, some of these, e.g., dry mouth and dizziness, were difficult to elicit in the smaller patients and often went unnoticed in older patients. The side effects listed are therefore largely the objective ones noted by the parents. Though some drowsiness was common it was rarely excessive or undesirable and in many instances it seemed helpful. It is interesting to note that drowsiness was found in 17 per cent of the patients receiving placebo therapy. Most physicians would agree that diseases associated with vomiting, especially the idiopathic gastroenteritis group are often accompanied by marked lethargy.

TABLE 6

SIDE EFFECTS ENCOUNTERED IN THE COURSE OF THERAPY OF VOMITING

Symptoms	Cases Treated	Side Effects Number	Per Cent
Chlorpromazine	155		
Drowsiness		56	36
Dizziness		3	2
Tachycardia		2	1
Dry mouth		2	1
Fainting		1	0.6
Meclizine	31		
Drowsiness		4	13
Restlessness		1	3
Cyclizine	17		
Drowsiness		3	18
Secobarbital	20		
Drowsiness		9	47
Placebo	29		
Drowsiness		5	17

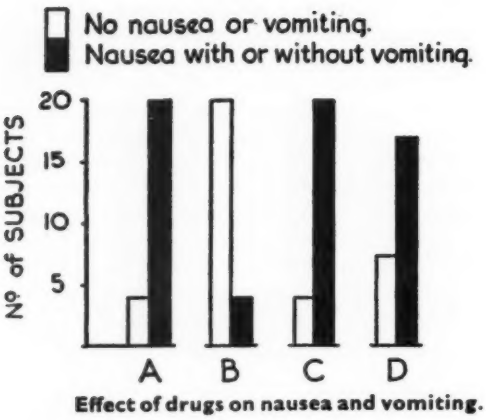
Discussion

Ideal management of vomiting should be aimed at correcting the underlying cause. In the practice of pediatrics, however, this is not always possible or, as in the case of antibiotic or nitrogen mustard therapy, vomiting may be unavoidable. There are therefore a rather large number of conditions associated with vomiting in children where antiemetic therapy is both effective and desirable.

Evaluation of the response of the individual patient to an antiemetic agent presents certain problems. Vomiting is frequently a self-limited disease. This is indicated by the good results obtained from placebo therapy. Other treatments such as parenteral fluids, antibiotics, and sedatives will alleviate contributing factors and thereby diminish the tendency to emesis. Our experience would suggest that barbiturate sedatives are not strikingly effective in this respect. To avoid the influence of fluids and antibiotics these were either not given or their administration was withheld until response to antiemetic therapy could be evaluated. In spite of these precautions there remains a reasonable doubt *whenever* uncontrolled clinical evaluation is the only criterion of efficacy.

In an effort to establish the value of chlorpromazine as an antiemetic agent for experimentally induced emesis, Isaacs[2] set up a critical double blind control study. Ninety-six clinical trials were performed in normal volunteer subjects. Each subject received all four medications in separate trials. The order of treatment was at random. "A" received a

FIG. 1

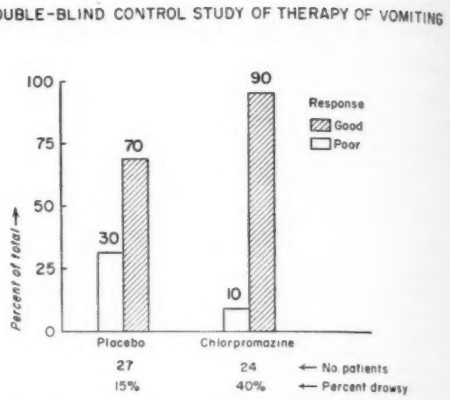


A double blind controlled study of the relative antiemetic value of chlorpromazine (B), promethazine (D), and placebo (A & C) in the control of apomorphine induced emesis. (From Isaacs[5]).

placebo, "B" chlorpromazine, "C" a placebo, and "D" promethazine. One hour later each subject was given a half pint of milk and 5 to 15 minutes later 1.0 mg. of apomorphine was injected subcutaneously. In this manner every volunteer received apomorphine four times, twice with a placebo and one each with chlorpromazine and promethazine. A representative graph from the author's work is reproduced as figure 1. The difference in response to the injections of apomorphine with placebo was studied and weighed in the final analysis. The protection offered by chlorpromazine is clear and could not be explained on the basis of a difference in individual response or tolerance to apomorphine, since the order of treatment was random.

Because of the paucity of controlled clinical studies of this nature we set up a double blind clinical evaluation of the influence of chlorpromazine in spontaneous vomiting. Rectal suppositories of identical appearance, containing chlorpromazine (25 mg.), inert substance (placebo), and Secobarbital (30 mg.) were used. The dose of medication is given in table 1 and the treatment schedule was at random. The physician dispensing the medication had no knowledge of the content of the suppository. After the therapeutic trial had been discontinued and the standardized data check sheet completed, a grade of response was assigned; only then was the medication entered on the data sheet. Figure 2

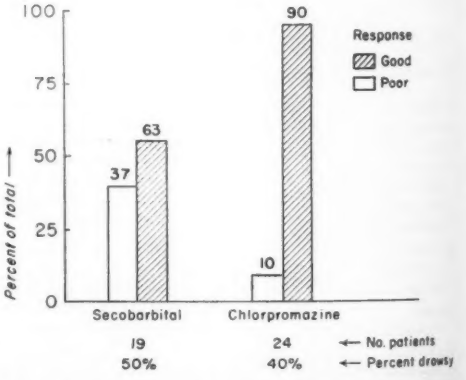
FIG. 2



A double blind controlled clinical study of the relative antiemetic value of chlorpromazine and placebo in the control of spontaneous vomiting in children.

illustrates the comparative response of chlorpromazine with placebo in this double blind study. The relatively high incidence of self-limited vomiting partially obscures the significance of the difference between the chlorpromazine and the placebo treated patients ($p=0.1$). However, when a treatment regimen is effective 90 per cent of the time it is likely to be of clinical value. The greater efficacy of chlorpromazine is similar to the findings in the larger uncontrolled clinical study (Table 3). Figure 3 is a similar comparison of chlorpromazine with placebo. The much higher response rate of chlorpromazine therapy is again evident and is statistically sig-

FIG. 3



A double blind controlled clinical study of the relative antiemetic activity of chlorpromazine and Secobarbital in the control of spontaneous vomiting in children.

nificant at the 5 per cent level ($p=0.05$) in spite of the relatively high incidence of self-limited vomiting probably present in this series, too.

Summary

The antiemetic drugs studied appear to be more effective in the control of vomiting than either Secobarbital or a placebo. The specific areas of indication and contraindication for the antiemetic agents are difficult to define rigidly. However, certain general guides may be useful.

Antiemetic agents are useful in:

Acute nonspecific gastroenteritis,

Acute nonspecific gastritis,

Vomiting associated with the therapeutic use of HN_2, antibiotic, x-ray, salicylate, etc.,

Vomiting secondary to acute infections, acidosis, emotional upsets, and chemical irritants.

Antiemetic therapy is probably not likely to be effective in:

Vomiting, associated with severe cough,
Increased intracranial pressure,
Organic gastrointestinal tract obstruction.

Antiemetic medication is probably ill advised or contraindicated in the following conditions:

Head injuries,
Jaundice and/or hepatitis,
Heavy sedation from other therapy,
Severe dehydration with shock,
Known hemopoietic depression.

If antiemetic agents are used with these considerations in mind and according to a suitable dosage schedule, they appear to be safe and useful agents in the control of vomiting due to a wide variety of causes. Their use represents a method of treatment for a symptom that if not promptly controlled may lead to rapid and severe dehydration.

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Parathyroid Hyperfunction: Diagnostic Difficulties*

JACK HYMAN, M.D., *Mobile, Ala.*

The author reviews the steps in the diagnosis of primary hyperparathyroidism, pointing out the difficulties in early cases unless accurate biochemical determinations are available.

THIS PAPER PROPOSES TO PRESENT A PROBLEM that we find is not ours alone and we hope to stimulate interest in some of its phases which may be of assistance in its solution. Parathyroid hyperfunction in this presentation will be limited to primary hyperparathyroidism, essentially associated with adenoma of the parathyroid gland, excluding from our discussion parathyroid hyperfunction induced by renal insufficiency and other states.

Our interest in primary hyperparathyroidism is motivated by our efforts to find the etiologic factor responsible for recurrent formation of urinary calculus in many of our patients. It is difficult to determine from published series what percentage of patients with recurrent calcium containing calculi might harbor parathyroid adenomas. In spite of the relatively large series of cases reported from major centers, it is our impression that the average urologist sees very few proven cases during several years of active practice. In the last five years of a community urologic practice we have seen five confirmed cases. In this condition, as in many others, one has to seek in order to find. Yet, in many instances, one can be led astray in his search through no fault of his own. The diagnosis of parathyroid hyperactivity is basically a laboratory diagnosis. There are a number of clinical findings which may be helpful in suggesting the condition but the preoperative diagnosis depends largely on laboratory data.

Physiologic Disturbances in Primary Hyperparathyroidism

I shall not burden you with the detailed physiology of the parathyroid gland nor attempt to review the several concepts of the mechanism of action of parathormone. It would be reasonable to follow the generally accepted concept of Albright[1] that the primary effect of parathormone is the regulation of the renal excretion of phosphorus, and the altered chemical changes associated with parathyroid hyperfunction ensue as a result of a disturbance in this process.

A functioning adenoma of the parathyroid would consequently initiate an increased excretion of phosphorous in the urine, which would decrease the level of serum phosphorus. Since ionizable calcium and phosphorus exist in the serum in a soluble state, the product of which is a constant, the fall in concentration of serum phosphorus demands a rise in the concentration of serum calcium. The hypercalcemia then results in increased excretion of calcium in the urine. Therefore, the significant abnormal chemical findings of hyperphosphaturia, hypophosphatemia, hypercalcemia and hypercalcuria will occur.

The elevated serum calcium and increased excretion of calcium creates a demand for calcium which must be supplied from the diet or from the principal endogenous source, the bones. When dietary calcium is inadequate, osseous decalcification occurs. As a result of this bone activity the serum alkaline phosphatase will be increased.

When these changes have been existent for a long period of time a fairly characteristic clinical picture is seen. Renal calcification occurs as part of this picture with or without disease of bone in about 80 per cent of cases.[2] About 60 per cent of cases show renal calcification alone.[3] The finding of peptic ulcer in about 15 per cent of cases is more than a coincidence. Hypercalcemia decreases the excitability of the neuromuscular apparatus so that muscular weakness, ease of fatigue, constipation and anorexia are frequent complaints.

*Read before the Section on Urology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

Cases of long standing with bony changes and renal calcification associated with marked alteration of the serum chemical values are really not difficult to identify. Extensive renal damage with impaired renal function and failure to excrete phosphates would reverse the hypophosphatemia and hypercalcemia, and might make it difficult to distinguish from a case of primary renal disease with secondary parathyroid hyperactivity.

Early Diagnosis

The prognosis is extremely poor when renal damage has been extensive even if a limited resection of an adenoma is done. In contradistinction to this, cases that are discovered early receive tremendous benefit from arresting this malignant process. This brings us to the essence of our discussion. Relatively early cases with small adenomas and mild chemical changes are difficult to identify. To detect the serum changes, accurate laboratory determinations must be done by interested and conscientious technicians. Consistent, accurate, calcium determinations are hard to obtain. The usual chemical test for serum calcium seems to have several sources of error and appears to be difficult to do accurately. The test for serum phosphorus has less room for variation and a careful technician should produce fairly consistent results. The flame photometer may be used for serum calcium determinations and may yield more accurate readings. However, considerable variation has occurred in determinations on known controls in our laboratory.

We have found a partial solution to this problem through the cooperation of our pathologist. One of our best technicians does all of the calcium and phosphorus determinations and doubly checks his results. The laboratory uses the "Proficiency Test Service" of Dr. F. William Sunderman of Philadelphia which supplies known controls to check methods and procedure.

If one has several determinations which are strongly suggestive of parathyroid hyperactivity, further evaluation with other tests must be done. Serum proteins should be considered in evaluating the serum calcium. Since total serum calcium is made up of ionizable and protein bound calcium, a marked alteration of the serum proteins can influence the estimation of calcium. Reduced serum protein may reduce the total serum calcium and mask an elevation of ionizable calcium; likewise an elevated serum protein could increase the total serum calcium yet the ionizable fraction might be normal. Since parathyroid hormone influences the ionizable calcium, the protein factor can be significant in borderline cases.

The serum alkaline phosphatase determination has no diagnostic value as far as parathyroid hyperactivity is concerned. Elevated values only signify increased activity in bone. Early changes in bone if detected are very helpful. Absence of the lamina dura of the teeth has been described as an early change and should be sought for.

The existence of hypercalcuria would appear to be a rather easy thing to evaluate, however it likewise has its limitations. Varying degrees of idiopathic hypercalcuria may be present in many patients who develop urinary calculi and in some otherwise normal individuals. The Sulkowitch test is a simple qualitative test for urine calcium. Two or three days of a calcium free diet should precede the test for accurate appraisal. There may be some discrepancy in grading the precipitate, however it can serve as a useful adjunct in the diagnostic screen. Twenty-four hour calcium excretion can be accurately measured. Yet, here again a useful test has its limitations imposed by technical accuracy and intestinal absorption of calcium.

Recently two tests have been used to aid in the diagnosis of parathyroid hyperfunction. Howard[4] and his associates have utilized an intravenous calcium test which reportedly gives a characteristic response in patients with parathyroid adenoma. Intravenous infusion of calcium in normal individuals is found to result in a rise in serum phosphorus and a reduction in the urinary excretion of phosphorus. The reduced excretion of phosphorus is explained on the basis of inhibition of parathyroid hormone by the hypercalcemia. In parathyroid adenomas the rise in serum phosphorus is much smaller, and the renal excretion of phosphorus is either increased or only slightly reduced. The variation in response is explained on the assumption that the adenoma is less easily inhibited itself and the normal parathyroid has already been suppressed by the functioning adenoma. Patients with small adenomas would apparently be

more likely to approach the normal response to intravenous calcium thereby making it difficult to evaluate the test in some early cases.

Schaaf and Kyle[5] have utilized a reasonably simple test which determines the per cent of tubular reabsorption of phosphorus as a means of detecting primary parathyroid hyperfunction. The hyperphosphaturia produced by parathormone seems to be associated with a marked reduction in the amount of phosphorus reabsorbed by the tubules. This can be determined by analysis of a four hour collection of urine for its phosphorus content, and determination of the serum phosphorus and creatinine midway between the collection period. One can consult the original article for the details of calculating the percentage reabsorption of phosphorus from this data. In normal individuals over 90 per cent was reabsorbed by the tubules, while only 50 to 65 per cent was reabsorbed in patients with parathyroid adenomas. The test is applicable to patients with normal or only mildly impaired total renal function. Marked impairment of renal function invalidates the results. We have not had the opportunity to apply it to a patient with a subsequently proven adenoma; however, in two instances patients with very suggestive chemical changes in the serum and clinical findings had a normal percentage tubular reabsorption of phosphorus. These patients were explored and adenomas were not found. We need more experience with these tests to evaluate their usefulness. Others should be encouraged to report their results so that an adequate series of cases can be collected.

It would seem obvious from the foregoing discussion that detection of patients with parathyroid adenomas has its difficulties. It would also be apparent that patients suspected of having an adenoma should be hospitalized for several days so that these various laboratory studies can be accomplished under adequately controlled dietary conditions. The added expense will certainly be justified before subjecting the patient to an exploratory operation. An operative exploration if adequately done is not a simple benign procedure, and the operating surgeon deserves every assurance of the existence of the adenoma from the results of our diagnostic tests.

Summary

1. The problem of detection of early cases of primary hyperparathyroidism remains a difficult one.

2. Serum chemical changes and urinary excretion studies are of great diagnostic value but reliable determinations must be done for accurate evaluation.

3. The intravenous calcium test, and the tubular reabsorption of phosphorus test may have considerable diagnostic importance, and their widespread application will permit better evaluation of their usefulness.

4. This damaging disease deserves early detection and treatment. The prognosis in late cases is extremely poor.

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Discussion (Abstract)

Dr. W. W. Sawtelle, San Antonio, Tex. Dr. Hyman is to be congratulated for his complete, concise and scholarly presentation of a problem in urology that is well known to all of us, but which can be easily overlooked unless the clinician keeps the entity constantly in mind when dealing with recurrent urinary tract calculi. He has left little to be added except possibly to enlarge on a few of the problems in diagnosis which have proved to be stumbling blocks for most urologists. The difficulty in obtaining reliable and accurate calcium determinations is not a problem peculiar to any one community or hospital. Indeed, it is almost a universal complaint the country over. Although I have no personal laboratory experience with which to substantiate my contention, I wonder if the difficulty in obtaining consistently accurate calcium determinations is justifiable. I am informed that the potassium permanganate method for the determination of calcium is one of the most precise tests in clinical chemistry, but it is apparently either not in widespread use, or is not supervised closely enough by our pathologists to insure its being performed correctly. The increasing use of the flame photometer is not an unmixed blessing since the method is more than a little tricky and demands a meticulous technic not within the training or experience of the average laboratory technician. Reliance on the values obtained by this method when not performed by an expert can easily lead to erroneous conclusions by the urologist.

The Sulkowitch test is a useful method for measuring the endogenous loss of calcium but as Dr. Hyman has mentioned, preparation with a calcium free diet is mandatory and in this connection it should also be emphasized that in many areas of the Southwest it is important to utilize distilled water for drinking purposes in conjunction with the low calcium diet.

Dr. Hyman has already emphasized the two most important points in the diagnosis of hyperparathyroidism: (1) the urologist must maintain a high index of suspicion in all cases of recurrent calcium stones; and (2) accurate laboratory studies by a competent laboratory under the direction of an interested, enthusiastic pathologist are absolutely essential.

In conclusion it should be mentioned that the task of the surgeon performing the exploration is not an easy one since in at least 10 per cent of the cases the tumor will not be found in the normal position of the parathyroids, but somewhere along the embryological path of the two branchial clefts which give rise to the parathyroids.

Dr. Robert Lich, Jr., Louisville, Ky. Dr. Hyman has presented most succinctly the problem of establishing a definite diagnosis of hyperparathyroidism. It is possible that this perplexing problem may be reduced by the use of the phosphorous renal tubular reaborption tests of Schaaf and Kyle or the intravenous calcium test of Howard. But, as Dr. Hyman said, a greater collective experience is necessary for the accurate evaluation of these newer diagnostic procedures.

The fallacy of our present tests for hyperparathyroidism lies in the fact that they are indirect measurements of parathormone activity and thus like any indirect measurement the opportunity for inaccuracy is prominent. Until we can measure the amount of parathormone in the blood directly the diagnosis of hyperparathyroidism will be troublesome.

A few words should be said on behalf of the surgeon exploring the parathyroid glands. It is our responsibility to prepare for him an accurate diagnosis. If the diagnosis of hyperparathyroidism is firmly established he can consider removing a parathyroid that shows minimal or even suggestive changes. However, if the surgeon is not assured of the presence of the disease he must cautiously avoid anything unless the parathyroid is typically altered. In other words, it is our responsibility and not that of the surgeon to make the diagnosis while it is his responsibility to discover the disturbed gland whether it reside in the neck or mediastinum.

May I say a word about establishing a positive diagnosis of renal disease when the problem arises as to whether or not the hyperparathyroidism is primary or secondary. This can, more often than not, be solved by renal biopsy with the use of a Franklin modification of the Vim-Silverman needle. Our experience with renal biopsy has been gratifying and I recommend it to you provided you are meticulous in its execution.

Dr. Hyman is to be congratulated on a well prepared and faultlessly presented paper on a subject that is of vital importance to all of us and our patients suffering with urolithiasis.

Benign Expansile Fibrous Lesions of Bone: Surgical Treatment*

G. W. N. EGGERS, M.D.,† *Galveston, Tex.*

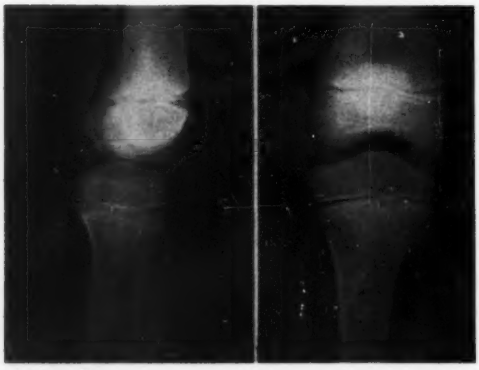
The author describes methods which may be used in the hope of controlling deformities in instances of expanding fibrous lesions of bone.

THE BEHAVIOUR OF BONE in the cycle of complicated metaplasia to form its mature structure has contributed many aberrations of immaturity resulting in abnormal structures of a benign and malignant nature. The relation of the so-called mesenchymal origin or fibroblastic precursors to adult bone results in many fibrous tissue formations of varying degrees and types. The term osteitis fibrosa has been applied to many fibrous lesions which have been gradually segregated into definite entities. The solitary bone cyst, hyperparathyroidism and related conditions have been separated from the inclusive group.

Monostotic Lesions

Another fibrous proliferation in bone which closely resembles fibrous dysplasia is the *nonosseous fibroma* (Fig. 1). Whether or not this is a true pathologic group or a variation of fibrous dysplasia must be decided by time and pathologic study. These usually involve a cortical area rather than the intramedullary portion but frequently protrude into the medullary cavity. These growths expand, cause pain (Figs. 2 to 4) and pathologic fractures (Figs. 5 and 6). The surgical treatment of the so-called nonosseous fibroma or monostotic lesions is removal of the fibrous mass. In this procedure it is noted that the reinforcement of the treated area is from the periosteum (Figs. 7 and 8). The monostotic fibrous dysplasia when similarly treated also presents the same periosteal reaction (Figs. 9 and 10). From this observation, the conclusion was made that in the more extensive involvement it could be possible to utilize the periosteal reaction to advantage in stimulating new bone formation to increase the strength and to improve the alignment of the affected bones.

FIG. 1



Solitary fibrous lesion or nonosseous fibroma of tibia in a child.

FIG. 2

Adult type of lesion of tibia as in figure 1. Only symptom was dull, aching pain.

*Chairman's Address, Section on Orthopedic and Traumatic Surgery, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Orthopedic Division Department of Surgery, University of Texas Medical Branch, Galveston, Tex.

Fibrous Dysplasia

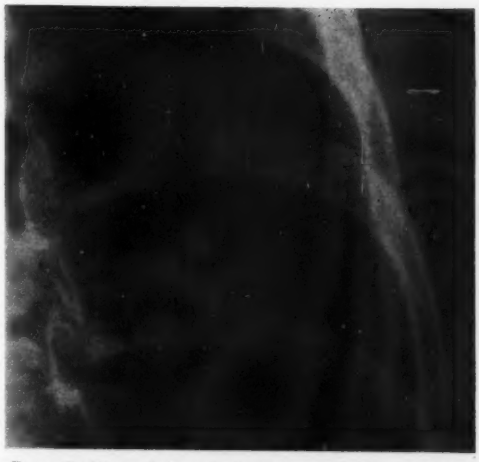
The condition termed fibrous dysplasia has also been individually identified. The group of cases of true fibrous dysplasia is interesting, and the present status of the condition is principally one of recognition and diagnosis. The occurrence of these fibrous conditions is usually noticed at about 8 to 12 years of age and is slightly more frequent in females. Some may present the typical Albright syndrome, but this is not true in all cases. Often, the condition is noticed because of a pathologic fracture. The condition may be monostotic or polyostotic and frequently tends to be unilateral (Fig. 11). In certain patients there may be present both central and cortical lesions when a bone survey is done (Figs. 12 to 14).

The x-ray appearance of the lesions may be said to be that of a thinning of the cortex with a tendency to bowing and loss of normal structure and trabeculation. The whole process may be termed slowly expansile due to fibrous tissue activity which in turn is due to the failure of the anaplastic fibroblast, for

FIG. 3

Monostotic fibrous lesion of fibula causing intermittent pain.

FIG. 4



Expansile fibrous lesion of rib. No roentgenologic evidence of lesion 3 years previously; pain only symptom; rib resected. Histologic diagnosis was fibrous dysplasia.

FIG. 5

Fracture through lesion of distal end of femur in child of 12 years. Cortical type of lesion.

FIG. 6

Fracture through fibrous lesion of tibia. Typical expansion of cortex. Same type of lesion as figure 1.

some unknown cause, to form mature bone in its metaplastic cycle. The result is that fibrous tissue, perhaps with slight variations in its cellular structure, proceeds in excess growth forming an expansile lesion. The expansile force in the medullary area combined with altered osteogenesis results in a bone with a thin cortex (Fig. 15) which may be easily distorted due to muscular pull and/or gravity, or may simply fracture. These basic features are accepted and then the consideration of the condition usually ceases.

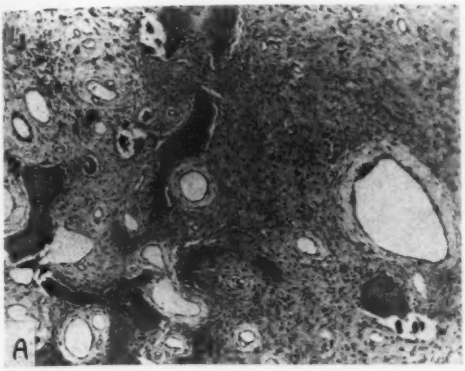
When these cases are considered clinically, a situation presents itself which demands some thought and consideration. Most of these patients are seen for osteogenic pain or for pain due to fracture. Most patients who have a deformity have accepted the condition as inevitable (Fig. 16).

The purpose of this presentation is to offer a thought and a procedure which may be of benefit in the early polyostotic cases. The approach to the subject has been based on the observation previously mentioned that the monostotic cases complaining of pain are relieved by surgical removal of the mass. It is certain that complete cellular removal is never accomplished, but the tendency of the condition to be less active as maturity is reached is a significant observation. This factor is utilized in preserving the additional

FIG. 7

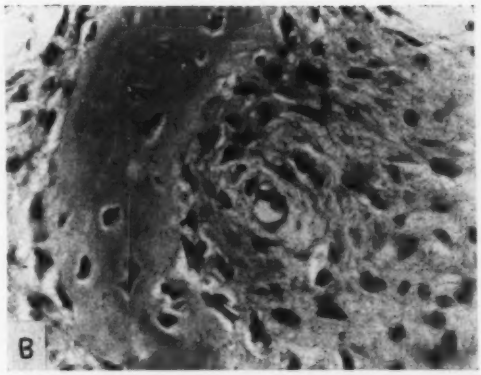
(A) Expansile cortical lesion of tibia. Pain and swelling 12 years. Preoperative appearance. (B) Local removal. Note periosteal new bone 5 months postoperatively. (C) One year postoperatively. Periosteal new bone adequately formed for strength, support and control of pain.

FIG. 8, A



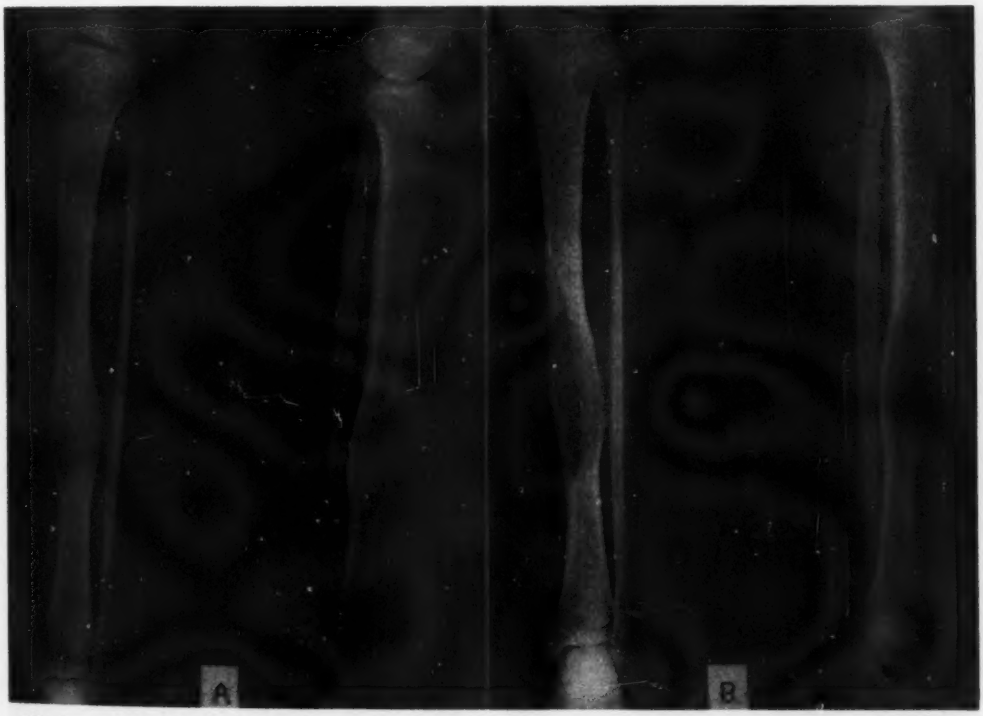
(A) Photomicrograph (X110) showing metaplastic bone formation. Multinucleated cells are osteoclasts. Histologic diagnosis of fibrous dysplasia.

FIG. 8, B



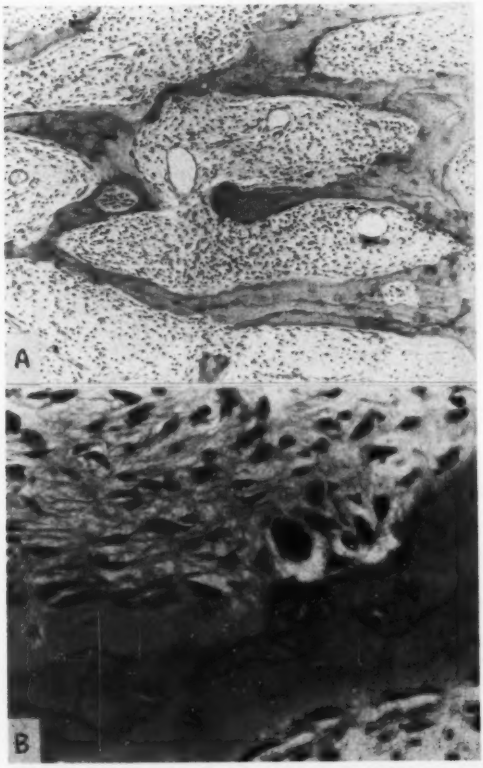
(B) Photomicrograph (X627) showing mature and immature fibroblasts. (From case in figure 7).

FIG. 9



(A) Expansile painful solitary fibrous lesion midshaft of tibia. (B) Postoperatively 3 months, note periosteal reaction to form new bone.

FIG. 10



(A) Photomicrograph (X110) showing metaplastic bone in lesion. Histologic diagnosis of fibrous dysplasia. (B) Photomicrograph (X627) showing immature and mature fibroblasts. (From case in figure 9.)

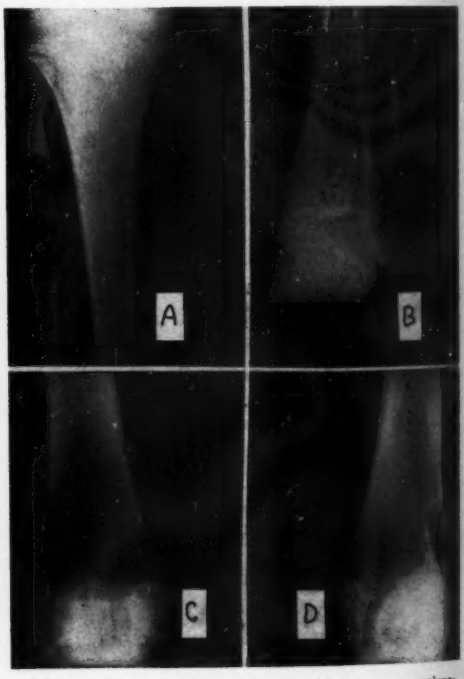
FIG. 11

Unilateral involvement of pelvis and femur by fibrous dysplasia.

cortex created by periosteal lifting. The removal of this expanding pressure has also been helpful in the relief of pain. The significant finding, however, has been that where the periosteum is raised or altered in the affected area, new bone is formed and the shaft thus strengthened. Having lost the expansile mechanical effect, this new bone persists and hypertrophies with the increased functional demands (Wolff's law). This observation has prompted the application of this mechanical procedure in earlier and more extensive cases. To be sure, one cannot expect new bone from the abnormal medullary area. The medullary cavity due to the fibrous changes is not a suitable bed on which to place bone grafts. They disappear in time and contribute little or no new bone in the area in which they are placed. Time and additional experience will be required for final evaluation of these observations.

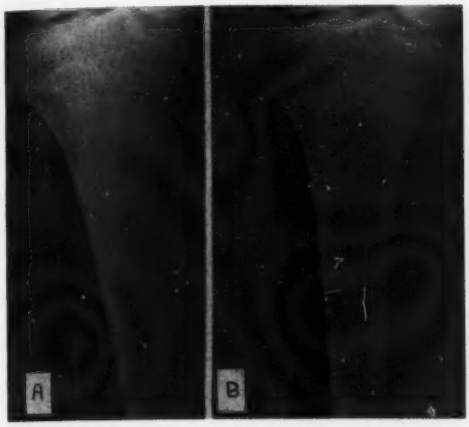
The approach for reduction of the expansile lesion and for periosteal stimulation

FIG. 12



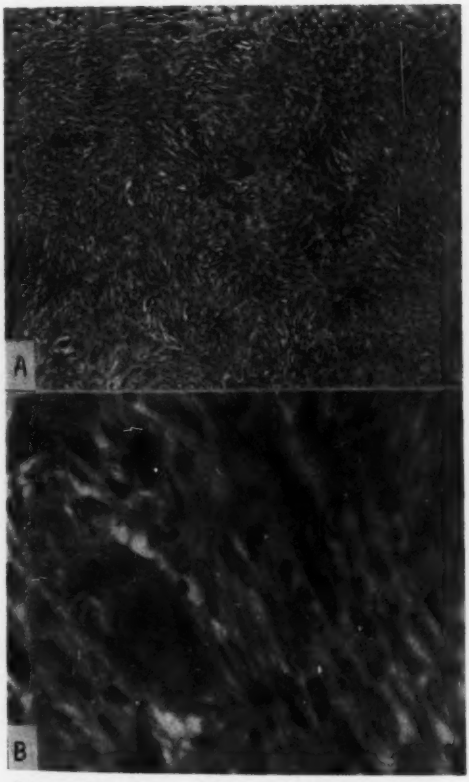
Multiple lesions, cortical and central, in same patient: (A) fibular central type; (B) tibial cortical type; (C) femur, left, distal end, cortical type; (D) femur, right, distal end, cortical type.

FIG. 13



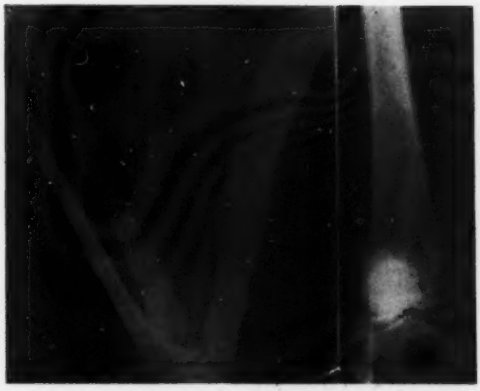
Fibula resected, with periosteal reformation of shaft: (A) preoperatively; (B) postoperatively. (From case in figure 12.)

FIG. 14



Fibrous tissue shows whorled and interlacing pattern; multinucleated cells are prominent. There is no metaplastic bone formation. These features are consistent with diagnosis of so-called nonosteogenic fibroma. (A) X110 (B) X627. (From case in figures 12 and 13.)

FIG. 15



Central fibrous lesions in adult showing little or no growth activity. Cortex thin, weak, and easily fractured.

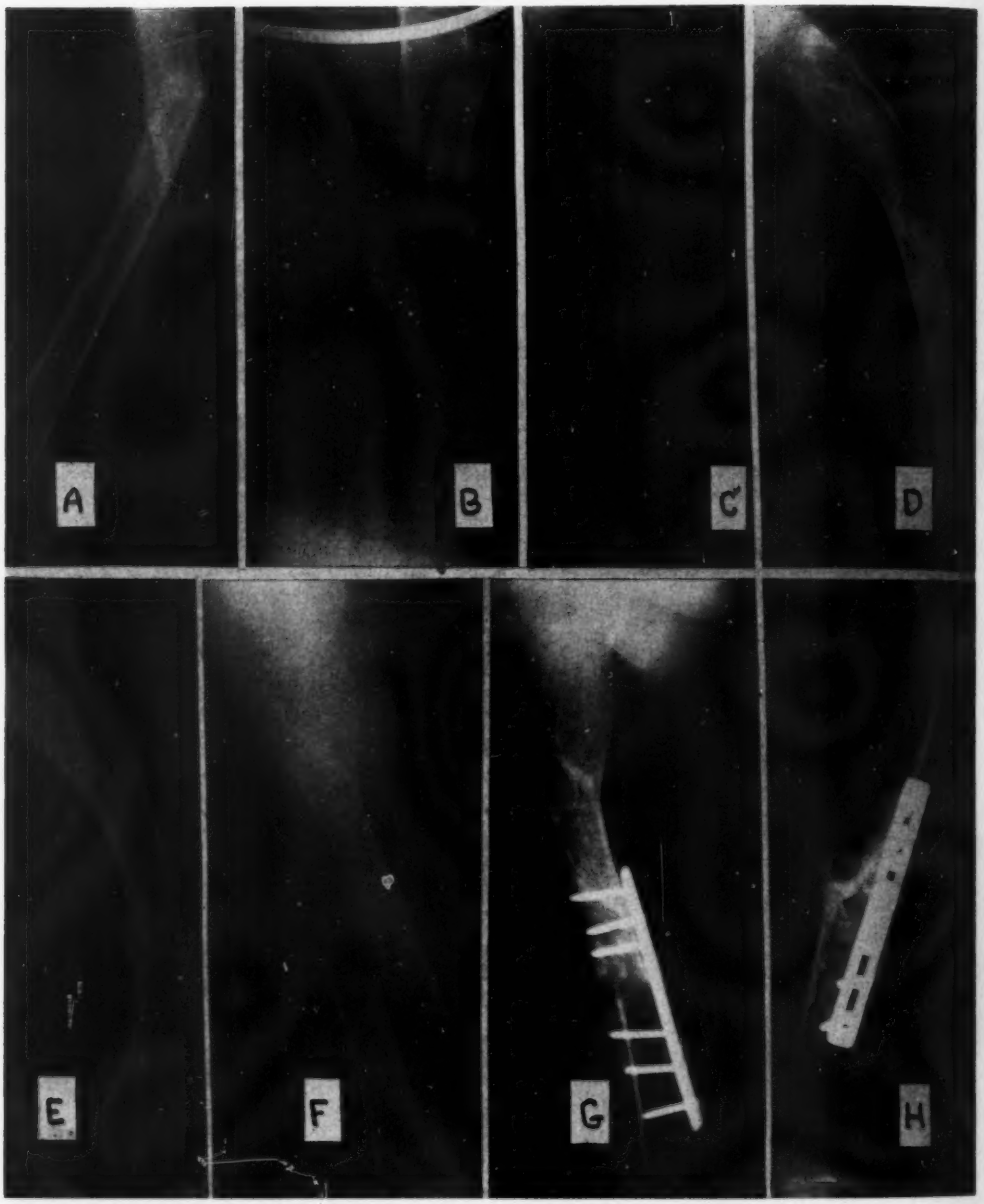
is surgical. The procedure is particularly necessary in the polyostotic cases where fractures and bone deformities may occur, and where it is desirable to reinforce the bone and to maintain alignment. We are aware of the limitation of our observation but offer it in the hope that others may ponder the propriety of it as well as the ultimate value.

The procedure as performed after diagnosis is to expose the affected bone. The cortex is opened by a longitudinal window to expose the contained fibrous mass. This tissue is removed as completely as possible, but it is realized that such removal cannot be complete from the cellular standpoint. Because the tendency is for slow reformation the expansile force of the fibrous tissue is long delayed. It is also accepted that the fibroblastic or mesenchymal cells of the intramedullary area are not expected to contribute mature bone to strengthen and stabilize the shaft or supporting osseous structure, nor is it responsive to grafts placed in the medullary cavity. Although there is no embryologic foundation for a variation in the quality of bone formed by the periosteum, it has been observed that the periosteum does respond by forming new mature bone whereas the intramedullary expanding portion does not form functional mature bone. The periosteum can and will form mature bone.* We offer no explanation as to why this occurs.

After the fibrous mass is removed mechanically and is examined by frozen section, we

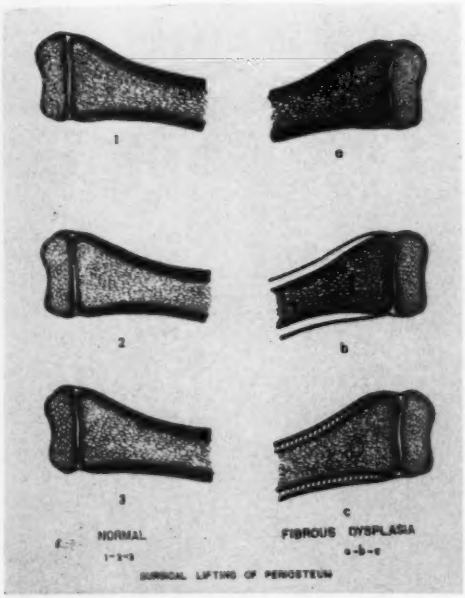
*See comment at end of paper.

FIG. 16



(A) Fibrous dysplasia, age 8, with fracture of upper third of femur. (B) Six weeks postreduction of fracture. (C) Fracture united 15 weeks after injury. (D) Eighteen months after fracture. Femur shows lateral bowing. (E) Two years and 4 months after first fracture. Progressive bowing with incomplete fracture midshaft of femur. (F) Two years and 6 months after first fracture. Midshaft fracture complete and displaced. (G) Reduction and fixation of midshaft fracture with chips and periosteal lifting, 2 months postoperatively, lateral view. (H) Anteroposterior view showing satisfactory union.

FIG. 17, A

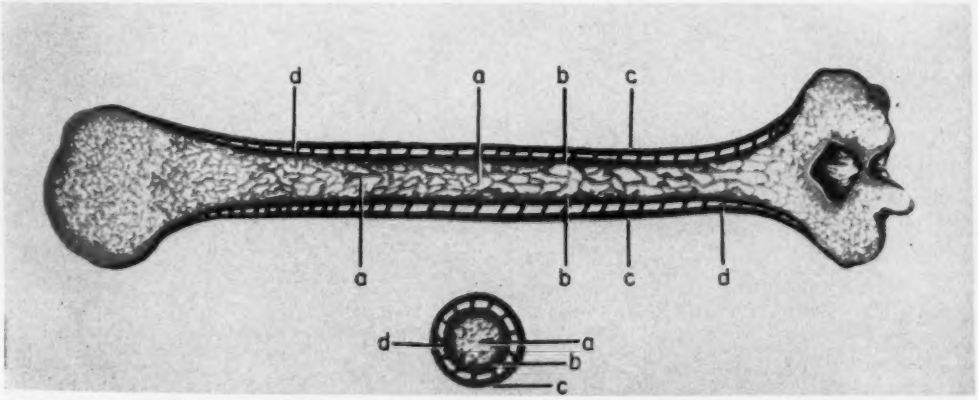


The surgical method of treatment by removal of the fibrous structure and periosteal lifting. (a) Fibrous expansion of medullary area with thin and weakened cortex. (b) Periosteum is lifted longitudinally. The expansile fibrous lesion is noted by arrow. The fibrous elements are removed surgically. (c) Expansion ceases after removal of fibrous elements; subperiosteal and periosteal new bone forms and creates a new shaft around the bone shaft which has lost its expansile force—area 0.

proceed to lift the periosteum extensively from the thin cortical bone around the entire length of the shaft (Fig. 17). It may be lifted in a fair sized sheet or in ribbon like pieces. At times, it tears because of structural weakness. We allow the hemorrhage to clot to create space between the periosteum and cortical bone. In this space the periosteum, fortunately, has created a new irregular encircling of bone capable of functional response and free of the previous expansile forces of the slowly growing intramedullary mass of fibrous dysplasia. Free of this force, the periosteal bone has developed to create a strong supporting structure. The result is not a bony structure of beautiful anatomic contours but a stronger functional bone, retaining the alignment present at the time of operation (Figs. 18 to 22).

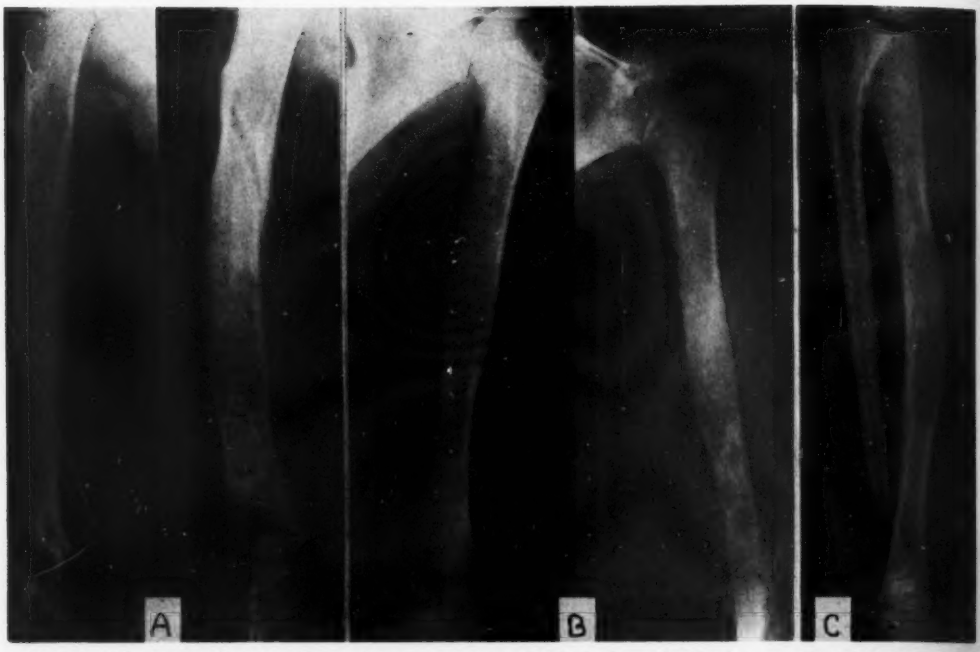
It is our thought that if these cases of fibrous dysplasia can be approached in this manner at an early age, many of the deformities will be diminished, total correction being doubtful (Fig. 23). In the absence of any other relief offered to those patients, such a procedure as described may be given consideration. Growth of the shaft would probably require repeated operations in the new portions of the shaft but would be justified.

FIG. 17, B



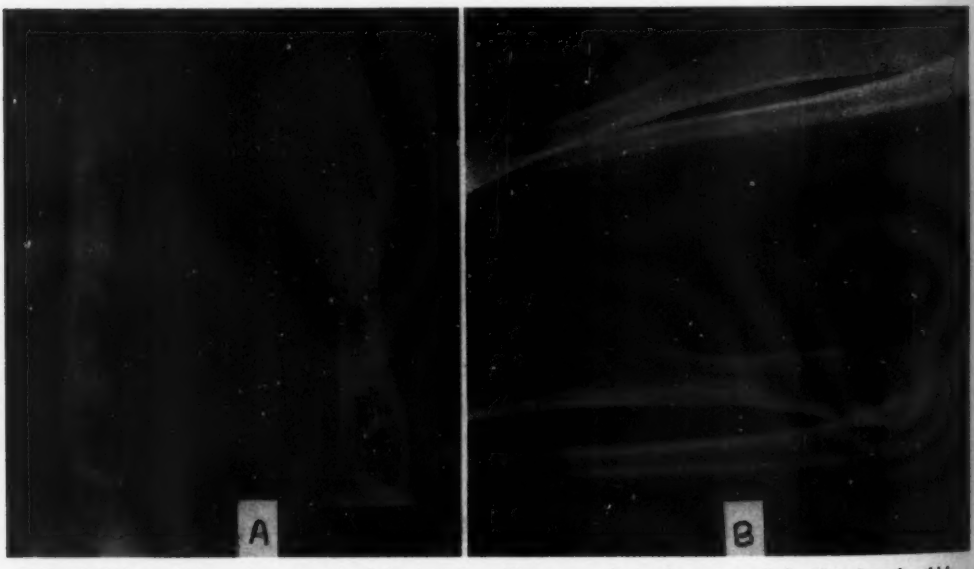
Surgical lifting of periosteum from shaft of bone. (a) fibrous dysplasia (b) thin cortex of shaft (c) elevated periosteum (d) area of clot formation between periosteum and shaft (blended grafts may be inserted between shaft and periosteum in the clot).

FIG. 18



(A) Polyostotic fibrous dysplasia. Preoperative roentgenogram of right humerus showing fracture. (B) Left humerus preoperatively. (C) Left forearm (radius) has fibrotic lesions—preoperative roentgenogram.

FIG. 19

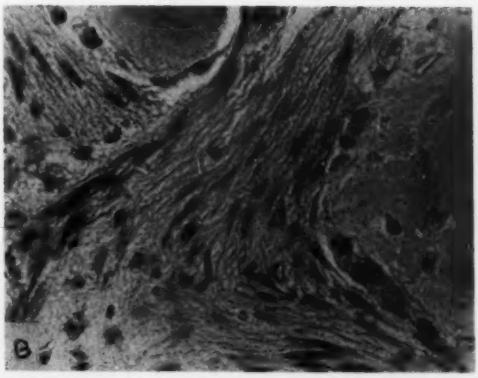


Periosteal lifting and incomplete removal of intramedullary fibrous mass, 5 months postoperatively. Note irregular thickening of cortex. (A) Humerus, right. (B) Radius, left. (From case in figure 18.)

FIG. 20, A

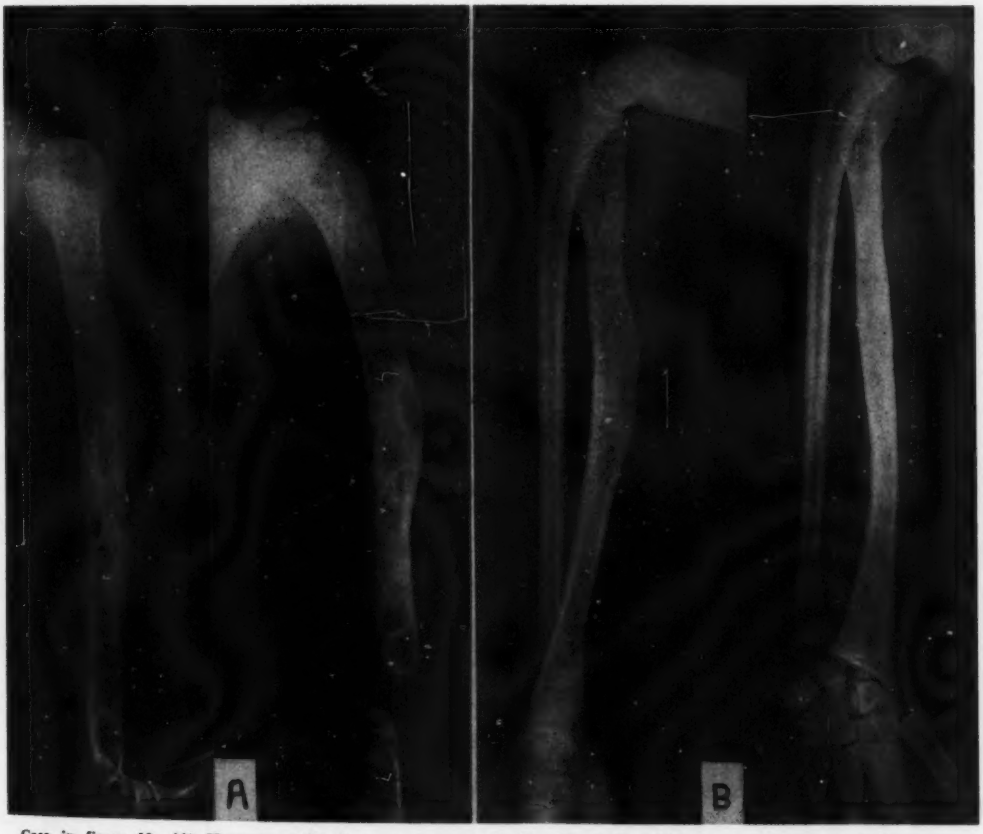
(A) Photomicrograph (X110). Histologic diagnosis of fibrous dysplasia.

FIG. 20, B



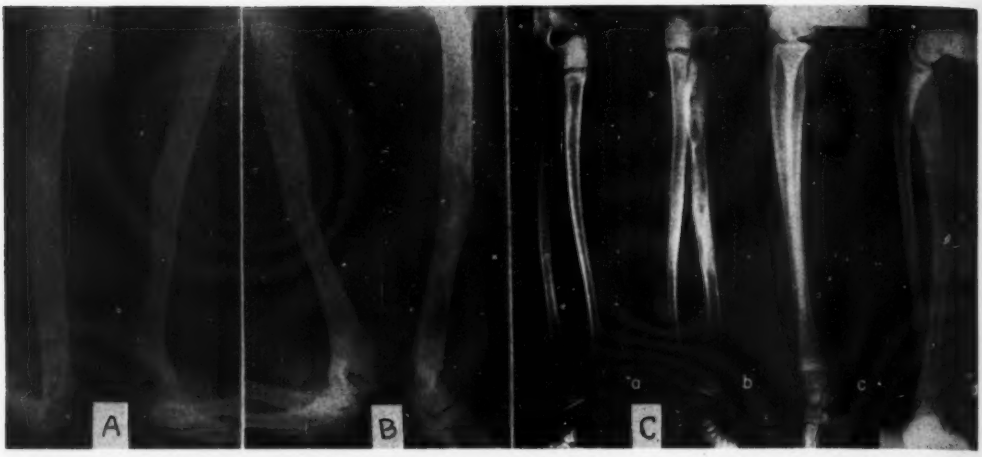
(B) Photomicrograph (X627). (From case in figures 18 and 19.)

FIG. 21



Case in figure 18. (A) Humerus, right, 8 months postoperatively. (B) Radius, left, 8 months postoperatively.

FIG. 22



Case in figure 18. (A) Humerus, right, 23 months postoperatively. (B) Humerus, left, 18 months postoperatively. (C) Radius, left, 23 months postoperatively. Note "b-d" left radius, for comparison with "a-c" the normal right radius. Note that the cortex has irregular increase of structure in these three views.

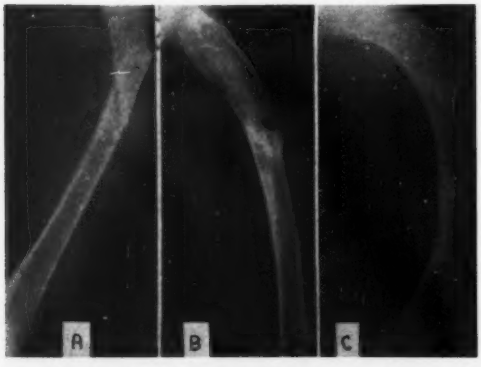
We have also altered our original periosteal lifting procedure, when possible, by trying to increase and form a layer of periosteal bone which would be greater in volume. This is being done by placing milled autogenous bone grafts between the periosteum and the cortical bone.

This is a preliminary report and is presented as such.

Acknowledgment

The author wishes to acknowledge with gratitude the kind assistance of the following: Dr. E. Burke Evans, Assistant Professor of Orthopedic Surgery; Dr. Charles M. Pomerat, Professor of Cytology; the Department of Medical Photography, the Department of Medical Illustration, and Miss Estelle Greenwalt, all of the University of Texas Medical Branch, Galveston, Texas.

FIG. 23



Case in figure 16. Femur straight prior to fracture. If periosteal lifting with or without grafts had been done in (A) at this stage, perhaps the bowing of (B) could have been decreased and condition (C) prevented.

Comments

Dr. C. M. Pomerat, Galveston, Tex. From the point of view of general morphology Dr. Eggers' implication that there is something very special about the architecture of the bony shaft, that it is elected and basic to the pattern of osteogenesis, is very attractive. The inquisitive student approaches the problem of osteogenesis in long bones with questions which invite further inquiry. "What sets off the mechanism of organizing a primary bony collar at the equator of the diaphysis?" Perichondrium around the cartilaginous model of the prospective bone becomes periosteum and periosteal ossification of the intramembranous type is substituted. Thus the periosteum is the determining factor for the process of forming long bones. "To what extent does the erosion of this protean bone by the lytic activity of endothelium and related agencies act as a cue for osteogenesis in the prospective marrow?"

Is it possible that the reaction set off by the procedure which Dr. Eggers reports for the treatment of fibrous dysplasia owes its success to the fact that it supplies a local traumatic stimulus with the necessary attending chemical factors to launch a process which was faulty in the initial history of the intracartilaginous ossification of the particular bone? Wounds reveal the organizational propensities of the body, but we often forget that morphogenesis occasionally is preceded by a natural wound in the history of development. If this be true, perhaps the rationale for the therapeutic measure which Dr. Eggers proposes depends on supplying a bony injury which a faulty development failed to provide.

Pneumoretroperitoneum Combined with Pyelography and Laminagraphy*

P. E. RUSSO, M.D., S. DOLIN, M.D., and
E. H. KALMON, JR., M.D.,† *Oklahoma City, Okla.*

The use of tomography along with pneumoretroperitoneum provides a most effective diagnostic tool whenever the situation justifies the increased hazard of irradiation.

THE RADIOGRAPHIC INVESTIGATION and detection of suprarenal and retroperitoneal disease have been hampered by the limitations of routine films of this part of the body, and also by the hazards of perirenal insufflation as first proposed by Carelli[1] in 1921. The danger of sepsis, air embolism, and the need for injection of each side separately have been more or less eliminated by the procedure of generalized subserous emphysema through a single injection as described by Ruiz Rivas[2] in 1948. This simple method to outline the retroperitoneal structures with air or oxygen may be combined with pyelography and laminagraphy with very little additional risk or distress to the patient. At the present time this combination of procedures is more or less reserved for well-selected cases which are suspected clinically of harboring some type of disease in this area. Clinical studies of a patient often suggest the possibility of involvement of the suprarenal glands or other retroperitoneal organs. An accurate diagnosis by radiographic studies will often show the size, location and extent of the tumor. Thus a more positive diagnosis is highly desirable prior to surgical intervention.

The first step in the study of these patients should be a routine film of this part of the body after proper preparation of the patient. This would consist of fasting for about 12 hours and cleansing of the colon with castor oil the day before. On such a film one may detect an abnormal soft tissue mass, an increase in density of a structure, calcium deposits, displacement or distortion of kidney shadows. It is well to remember that accessory adrenal glands are found in about 32 per cent of cases in the celiac area between the two kidneys.[3] Oftentimes this routine film may give no, or indefinite information. Further investigation with precoccygeal air or oxygen insufflation is then carried out. About 1,200 to 1,500 cc. of gas is used to outline the retroperitoneal structures more sharply. Usually fluoroscopy is done following the injection, and when proper distribution of the air is obtained films including oblique and lateral exposures are made. If these films prove satisfactory, and more detailed studies are to be carried out, intravenous pyelography is done. Usually a single film is taken at 6 to 10 minutes after the completion of injection of the contrast media. Following this laminagrams at 0.5 to 1 cm. levels are taken throughout the entire thickness of the kidneys. The question of radiation exposure arises in the patient who undergoes such an examination. However, most of the retroperitoneal diseases are a serious threat to the patient's life and a fairly good percentage of cures result from their surgical removal. Thus, an accurate diagnosis justifies the radiation exposure and other risks to the patient.

Since the radiologist is now called upon more frequently to detect changes in the retroperitoneal structures, it behooves him to have a thorough knowledge of the normal appearance of these organs and their variations. To accomplish this we hope to carry out this combination of radiographic procedures on patients with incurable malignant tumors in whom there is a fairly high percentage of metastases to the kidneys, suprarenal glands and retroperitoneal lymph nodes. Correlation of x-ray and autopsy findings, would in our opinion, give valuable information in this subject.[4]

*Read before the Section on Radiology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the University and Crippled Children's Hospital, and Wesley Hospital, Oklahoma City, Okla.

Case Material

A few illustrative cases with a brief history and findings are presented.

Case 1. C. C., a 52 year old white man, was investigated for an indefinite mass in the left side of the abdomen with pain over this area. Radiographic studies failed to uncover any disease of the retroperitoneal organs. The pneumoretroperitoneum was normal.

Case 2. C. L. C., a 55 year old white woman, had been operated on two and a half years previously for a malignant tumor of the corpus uteri. A mass which could be separated from the liver developed in the right upper quadrant. Air studies on the pateint revealed a metastatic tumor posterior to the right lobe of the liver which was surgically removed. It proved to be a metastasis from a leiomyosarcoma.

Case 3. N. T., was a 50 year old white man who was admitted because of considerable weight loss, weakness and an indefinite mass in the left upper quadrant. An upper gastrointestinal series showed evidence of extrinsic pressure by the mass along the greater curvature of the stomach with some anterior displacement suggesting a tumor of the pancreas. Air studies revealed that the retroperitoneal structures on the left side could not be outlined by this method. At operation a tumor of the tail of the pancreas was found which was adherent to all the retroperitoneal structures on the left side and therefore inoperable. The diagnosis was metastases from carcinoma of the pancreas.

FIG. 1

(Case 8) Multiple suprarenal tumors. One large tumor is seen on the right side and two tumors, both fairly large, were found on the left side.

FIG. 2

(Case 9) Pheochromocytoma of accessory adrenal gland. A smooth soft tissue mass is seen in the paravertebral area. Size of this tumor was 6 by 8 by 6 cm. (By courtesy of the Ann. Int. Med. 41:131, 1954.)[10]

Case 4. E. W., a 49 year old negress had anorexia, progressive weakness and anemia, with a mass in the left lower quadrant. Air studies in this case, although they were not absolutely necessary for the correct diagnosis, clearly outlined the enlarged left kidney,—a hydronephrosis.

Case 5. D. R., a 14 year old white boy had a weight loss of 50 pounds in the past 3 months, and a palpable mass in epigastrium. Plain film of the abdomen and a complete gastrointestinal series gave no clue as to the nature of the mass. Since a retroperitoneal tumor was a possibility in this case air studies were done. The great loss in weight in this patient made it possible to feel a horseshoe kidney through the abdominal wall. The loss of perirenal fat made it impossible to make this diagnosis on films of the abdomen. The diagnoses were anorexia nervosa and horseshoe kidney.

Case 6. I. P., a 61 year old white woman had a painful mass of long duration in the right lower quadrant. Although disease of the kidney was suspected in this case, air studies outlined the smooth mass attached to the lower pole of the right kidney. The diagnosis was cyst of the kidney.

Case 7. B. N. This was a 34 year old white woman who showed obesity, hypertension, diabetes, hirsutism, striae of the skin and a "buffalo hump" and was suspected of having an adrenal tumor. The 17-ketosteriods were elevated, as were, also, the 11-oxysteriods. Air studies revealed bilateral enlargement of both

adrenal glands. Recently this patient was placed on Metacortin, the diagnosis having been made of Cushing's syndrome with adrenal hyperplasia.

Case 8. J. V., a white man aged 39 years, complained of painful urination, hematuria and elevated blood pressure. A suprarenal tumor was suspected. Air studies revealed tumors in both suprarenal areas. At operation one adrenal tumor was found on the right side, and on the left side two suprarenal tumors were removed (Fig. 1). The diagnosis was multiple suprarenal tumors.

Case 9. C. R., a 14 year old white boy gave a story of the sudden onset of headaches and projectile vomiting of about 4 months duration with 20 pounds loss in weight. The blood pressure was 220/190 mm. of Hg. A pheochromocytoma was suspected. Air studies revealed a tumor mass 6 by 8 cm. in size located in the right para-aortic region. At operation this mass was found to be located between the aorta and inferior vena cava with the right renal artery located over its anterior surface (Fig. 2). This was a pheochromocytoma of an accessory adrenal gland. (This case has been reported.[5])

Summary

In cases in which there is a clinical suspicion of disease of any retroperitoneal organs, routine x-ray studies may be supplemented with the combined procedures of pneumoretroperitoneum, intravenous pyelography and laminagraphy to obtain more detailed information concerning these structures. Although this procedure is fairly well accepted for visualization of the suprarenal glands,[6-8] it may also prove very useful in the study of benign and malignant tumors of the kidneys,[9] and also for other retroperitoneal tumors or metastases. We have found, as our experience with this procedure has increased, that our ability to detect significant changes has improved. Further correlation with surgical and pathologic material will further improve our diagnostic acumen.

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Discussion (Abstract)

Dr. Martin Schneider, Galveston, Tex. Roentgenographic exploration of the retroperitoneal soft tissue structures took a giant step forward with the demonstration of the effectiveness and *relative* safety of presacral pneumoretroperitoneum. This method of contrast study has been widely adopted in this country now, and Dr. Russo has pointed up concisely the wide range of usefulness of this method in studying the normal and pathologic changes in the soft tissues of the paravertebral structures, retroperitoneal lymph nodes or other masses in the para-aortic zone and, of course, the extremely important delineation of renal and perirenal lesions. In our experience, at the University of Texas Hospitals in Galveston, this method has just about completely supplanted perirenal insufflation in most of the cases studied in the past two years.

Differentiation of the various normal soft tissue structures may yield the most fruitful results if we are able to separate well the various muscle groups and vascular structures which, in the ordinary anteroposterior film of the abdomen, are distinguished from each other poorly, if at all. As for the combination of this method with tomography, I want to commend Dr. Russo for his moderation in advising that it be used only in selected cases for definite indications. Used routinely, as some workers apparently suggest, we would all too frequently be "gilding the lily" and subjecting our patients unnecessarily, to perhaps added expense and radiation exposure. I believe that most pneumoretroperitoneum studies reveal diagnostic findings without tomography, and only occasionally do the tomograms yield additional significant information which would make a difference in the medical or surgical management of the patient. We should therefore employ body section films sparingly with these other methods by individualization of each diagnostic problem. Certainly such tomograms produce striking radiographs and it must be tempting to use them more often because of this factor. In conclusion I want to congratulate Dr. Russo on this terse and well-presented group of cases, bringing to our attention again an improved method of contrast radiologic study in an area of the body otherwise difficult to examine adequately.

The Use of Reserpine in Cerebral Palsy*

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The author proposes the use of reserpine in children having cerebral palsy for the control of emotional reactions which at times interfere with rehabilitative physical and similar therapies.

THE CHILD HANDICAPPED BY CEREBRAL PALSY requires a holistic approach rarely surpassed in medicine.

Seldom does one have to recognize and handle such a diversity of functional abnormalities as arise when the brain is damaged prior to maturity. Neuromuscular dysfunction, musculoskeletal deformity, intellectual impairment, cerebral dysrythmias and emotional instability (to and including the catastrophic reaction), all occur as a direct consequence of the damage to the higher centers.

The therapeutic efforts in cerebral palsy may be directed at:

1. Development of muscle coordination.
2. The teaching of skilled movements.
3. The development of substitutive technics.
4. The correction of deformity.
5. The reduction of emotional tension handicaps.

Emotional Reactions in Cerebral Palsy

Throughout the work with the cerebral palsied individual, one must recognize and deal with the influence of the emotions on the other therapeutic efforts.

Training may be handicapped by the tension present in the child as a result of his previous difficulties in interpersonal relationships.

On the other hand we recognize that the patient may, because of his tendency to overreact in any effortful situation, develop such an amount of tension that training is impossible, not as a result of basic incapacity to learn, but simply because of the disabling effect of emotionality.

In addition to the more or less purely neurologic defects there is the increased amount of tension as a result of unsuccessful effort and of fear. The reaction to the inability to complete a task is optimally perseverance; on the other hand it may result in an emotional discharge or discontinuance of effort. In the last there is a likelihood that training will be seriously handicapped. This is the area of tension with which we are primarily concerned in this study.

We recognized in our treatment center a number of children who seemed to be capable of deriving more benefit from the physical therapies than they were obtaining. The psychiatric consultant had frequent referrals from the staff therapists with a comment such as this, "We feel that little can be done for this child until he has some help with his emotional problems." In other words they realized that emotional tension was seriously handicapping their efforts. It might be said that this tension, as it is expressed through the neuromuscular system, acted as effectively in limiting the child as would muscular contracture or deformity.

We felt it imperative that we utilize all technics that might be effective in handling this type of disability. We recognized that although the problem was basically an emotional one, interview type of psychotherapeutic measures were not particularly effective. Among the reasons we had been able to offer so little psychotherapeutic help were: (1) lack of time for psychotherapy; (2) difficulties in communication; and (3) limitations of currently available psychotherapeutic technics.

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The author wishes to express his appreciation to the staff of the Cerebral Palsy Center for their assistance in this study.

The drug, as Serpasil, for this study was supplied by Ciba Pharmaceutical Company.

We thus began a search for any agent which might facilitate the treatment of the child under one or another of the training therapies.

Drugs in Control of Emotional Reactions

The drugs which have been used in an effort to relieve the tension include: the barbiturates, synthetic curare-like drugs, Prostigmin, aneleptics, alcohol and the anti-epileptics.[1] None of them is without disadvantage. The sedatives reduce tension, but also reduce the child's alertness and therefore interfere with learning. The curare-like drugs if used in sufficient dosages reduce the degree of muscle reactivity, but at the same time reduce the responsiveness of the musculoskeletal system to central impulses.

The anti-epileptics are effective at least in part as a result of their sedative effect.

Alcohol in spite of numerous advantages has some of the disadvantages of the barbiturates.

The ideal agent appeared to be one which induces a state of tranquility without sedation, in which alertness is unimpaired, but anxiety and concern over failure is diminished.

We have been searching for such a drug and this paper is based upon our clinical experiences with reserpine as an adjunctive therapeutic agent in the treatment program of an outpatient Cerebral Palsy Center. The drug was used initially because it was thought that it might be of benefit to some of the children who were not responding to the usual treatment procedures at a rate considered to be near their maximum. An investigation of the drug itself was a secondary interest. Although there appeared to be good evidence that the drug might be effective, and perhaps warranted a full scale controlled study, we did not feel that we were justified in undertaking such a project in our treatment facility. An uncontrolled study would, in our mind, offer a scatter of results which might help us select the type patient most likely to respond and, therefore, be more suitable for an intensive research program. Because of this we make no effort in this paper to prove by control studies, or statistical methods that the drug was effective. We will on the other hand simply report our findings with the group under treatment in the hope that some logical assumptions may be arrived at. If such assumptions appear to justify further investigation, statistical studies may be undertaken to satisfactorily confirm or disprove such assumptions.

We received reports from a number of sources which stimulated and sustained our interest in this study.

Kirkpatrick[2] had reported that reserpine had been effective in a number of instances in reducing the muscle artifact on electroencephalographic tracings. We felt that this definitely indicated a possibility of action at the discharge level.

Faust[3] had used the drug with good results in an adult with cerebral palsy, hospitalized because of psychiatric problems. Here again was an indication that the drug justified study.

The use of the drug in psychotics[4-6] indicated a reduction in concern over content, and this we thought might be considered to be analogous to thoughts concerning failure in the training efforts.

Theoretically there are a number of ways by which the drug might favorably influence the cerebral palsied child: (1) a direct effect on the neuromuscular system; (2) a general tranquilizing effect; and (3) a reduction of the patient's responsiveness to frustrating or anxiety, creating situations.

The patient group upon which this study was made are children under treatment at a volunteer agency. The Center is financed through the United Fund and the active backing comes in a great part from the parents of the children themselves. The medical staff is an unpaid consultant group. Although a number of the children are private patients of one or other consultants, the chief worker in this study did not have either a child, or parent in this group as a private patient.

The treatment was offered to the parents, and although there was verbal acceptance in all cases in this study, we are aware that in many cases the medication was given quite irregularly. It is our belief that if controlled studies are done it should be while the children are hospitalized to insure that the prescribed treatment program is actively followed. Only in such instance do we feel that statistical results approach any validity.

The treatment program of the children to whom we gave reserpine was somewhat varied; some of the children were on an extremely limited home program, all of whom were

considered to be so handicapped that treatment at the Center was not indicated. The other children were receiving one or another type of therapy at the Center, occupational, physical, and/or speech therapy. A number of the children were recognized to have clearly defined emotional problems.

Use and Effects of Reserpine

The impressions of the effect of reserpine are based upon the opinions of a number of observers: (1) the parents, (2) the psychiatrist (3) the therapist—occupational, speech, and physical, and (4) in some cases the patients themselves.

The group consisted of 15 patients, two of whom discontinued treatment shortly after it was begun. In both cases there had been obvious reluctance in the responsible parent to start the child on medication, and with the development of slight symptoms which might have been complications, the drug was dropped. One mother indicated a desire to institute treatment at a later date. The patient was an asthmatic and the drug was begun during his period of asthma. He developed tightness in the chest shortly after taking the first dose.

The other child, as reported by the mother, became extremely upset emotionally, coincident with beginning the drug. She only casually mentioned the death of the child's grandfather at the same time the drug was started. The mother, however, felt the drug was responsible for the change in the patient's condition.

All other patients continued on medication for what we consider to be a fair therapeutic trial.

The parents were asked to comment upon the effect of the drug. The therapists were asked for a general comment, and then to make a simple statement as to whether or not they noted changes in: (1) tension, (2) cooperation, (3) emotionality, (4) perseverance, and (5) treatability.

It is worthy of note that the parents seemed considerably more impressed by changes in the patient's behavior at home than were the therapists in the treatment Center. Their comments were more concerned with the child's relationship to the environment than with any observable changes in the patient's motor function.

Comments, such as: little easier to handle; more cooperative; more relaxed; more playful; walks more; easier to dress; and can sit more quietly so toilet habits are better, were common from the parents. Perhaps the most positive comment is in relation to the greater ease of handling the patient.

Patients selected for treatment during the initial stage of therapy included a high proportion of children who were thought by the therapist to display a severe degree of emotional instability. The selection reflects to some extent the therapist's pessimism, and one might say even desperation. The therapist, sensing the potential that is not being utilized, generally develops more tension than with the child who is more obviously restricted. This same sort of tension is noted in the parents of many of these children. Human nature being what it is, this tension is in many cases transmitted to the child, thereby, increasing the difficulty of treatment.

Although there were some comments indicating a degree of change under medication in all patients, a number of the patients did not maintain the initial improvement.

Others responded to a slight degree and have continued to retain that degree of improvement to this time.

A third group showed a greater response and have retained any gains they made.

The fourth, the group affected most impressively is that having frank psychiatric problems, and/or of overactive children.

The 15 patients have been divided into the following categories:

1. Discontinued—2 cases. Both had an athetoid situation and were in the older age group. They were relatively inactive and on superficial psychiatric examination did not offer evidence of more than minimal psychic discomfort.

2. Change not sustained—3 cases.

3. Change sustained but of minimal degree, and of questionable significance—2 cases. These groups, whose change appears to be of questionable significance, appeared to be relatively comfortable in the treatment situation prior to the administration of the drug. The fact that the chief improvement is noted in their interpersonal relationships outside the center makes it seem possible that unrecognized psychic discomfort was present.

4. Change sustained and possibly significant—3 cases. This group appeared relatively comfortable but showed marked striving toward activity and accomplishment. They were of good intelligence and were extremely concerned with their disability.

5. Change sustained and of definite significance—5 cases. This group with the greatest degree of improvement had definite evidence of psychic discomfort in the treatment situation as well as in all their relationships prior to the administration of the drug and this discomfort was notably reduced under medication.

The fact that the parent noted more relaxation and general improvement than the therapist, could be explained in that the therapist's relationship with the patient is in a structured situation in which there is less likelihood that interpersonal tensions would arise than at home. Perhaps the parents see more because there is less tranquility in the home than during the treatment session, thus increased tranquility would be first noted there.

The most favorable results occurred in 5 of the children whose limitation was most strikingly due to something other than motor disability. Two of the 5 were markedly hyperkinetic. In the other 3, the frank psychiatric nature of the disability with much surface tension was obvious.

This finding would tend to be in accord with the results that might have been expected from the experiences with the drug in other conditions.

Case 1. A 13 year old girl had athetosis and good intelligence but severe emotional disturbance. This child responded extremely poorly in therapy. She reacted violently to any sort of pressure, bursting into tears or protesting incapacity. She was placed upon medication with gradually increasing dosage and the mother's impression was that the child was more relaxed both physically and mentally. She did not show marked relaxation during her treatment session, but she did appear willing to exert more effort than before, and to tolerate more discomfort. In her relationship with the therapist she was definitely less prone to irritability and hostility.

The patient states that she feels better, and her general appearance is less one of unhappiness.

Case 2. A 6 year old boy had had a period of cyanosis and unconsciousness 5 days after birth. Petit mal seizures began at about six months of age. The patient has been under Tridione medication and has only occasional seizures. He had some weakness of the left side and was enrolled in nursery school at the Cerebral Palsy Center.

Throughout the three years of the child's attendance at the Center little constructive work was done with him. He was at first extremely overactive, tearful, loud and destructive. This became less as time went on, but the child never learned to play with other children. If left alone he would become extremely upset, would lie on the floor and pound his head. This was so severe that he constantly wore a helmet.

Hand-biting had been such a problem that corns developed upon the hand, hair pulling was also a problem. The child would destroy books or papers that came within his grasp. On many occasions it appeared that the child was out of contact with the environment.

EEG tracings were indicative of focal abnormality in the right temporal and occipital lobe.

The diagnosis was felt to be cerebral dysrythmia and possibly schizophrenia.

The child was placed upon medication in the hope that he would become less of a management problem. The demands he made upon the parent and the nursery school teacher meant almost constant attention; if not met one of the self-mutilative technics would come into play.

With gradually increasing dosage of reserpine up to 6 drams of the elixir daily, he showed considerable reduction in activity, and the self-mutilation has been reduced. The child is still demanding, but if his demands are not met he does not respond so violently.

I have attempted play therapy with this child and have so far been unsuccessful. I may note that on one occasion recently he told me good-bye, calling me by name for the first time in our three years' experience.

The mother states that he is much easier to manage. He was taken on an automobile trip of 2,000 miles during the summer and remained fairly quiet.

We feel that there is evidence of more intellectual capacity than was recognized before the use of the drug.

Case 3. A 10 year old girl, having athetosis, had been under treatment at the Cerebral Palsy Center for three years. She had a severe emotional disturbance, was fearful of new endeavor, and made constant demands for reassurance upon the therapist. Individual initiative was slight.

In addition to this handicap her psychologic test indicated that she was not keeping up and there was a drop in her test score from 72 to 50 in a two year period. Observation of the child lead the psychologist, therapist, and psychiatrist to believe that the child was functioning far below her capacity.

She was placed upon medication and became more relaxed in her attitude toward therapy. She demanded less reassurance, and would more willingly undertake new activity. This relaxation was not constant, but it is felt that she does show a sustained effect from the drug. There has been a moderate increase in her purposeful activity.

Case 4. A 6 year old, spastic boy, with marked diffuse cerebral dysrythmia, was a severe management problem both in the home and in nursery school. Training was practically impossible because of his distractibility. He would run from one thing to another, and could not be held to any task.

His mother describes him as being "wild." On medication the child became more relaxed, would sit for a few moments and play with his toys, and became less destructive.

He is not now under therapy, but his mother makes the following comments: "Not as wild as he used to be, doesn't run as much. Plays more with his toys, is easier to handle."

We see little evidence that the effect of the drug is on the primary neurologic defect, rather it seems to us that the patient is able to function somewhat more comfortably in spite of the defect and continue beyond the point which would have previously resulted in failure and development of incapacitating tension.

It seems also, without having sufficient data to prove it, that the anxiety so frequently seen is reduced. One of our children, previously fearful of falling and who would not attempt independent walking, is now willing to take the step.

One of the most pertinent comments on our use of the drug was made by a 14 year old patient who commented, "I feel better." This state of relative well-being may be the primary benefit that comes from the use of the drug. "Feeling better" has implications both for treatment and for the over-all well-being of our patients. The life-long use of the drug certainly is not desirable but the vistas opened by a state of psychologic comfort will possibly permit a far reaching re-orientation of the patients activities. It is our hope that this "Feeling Better" will result in willingness to expand activities and to continue in such activities in spite of initial frustrations until they have been mastered.

Complications Noted. The drug was discontinued in one child because of an exacerbation of a seasonal bronchial asthma. Diarrhea occurred in three children. One child developed a mild erythematous eruption on the wrist. In many of the children "grogginess" was a complaint until the medication was adjusted.

Range of Dosage. Dosage ranged from 0.25 mg. daily to a high of 4.0 mg. daily, and was determined by trial in the individual child. Routinely a low beginning dosage was used gradually increasing it until a maximum benefit was reached; from that point the dosage was then reduced to where the minimum dosage for maximum effect was reached. The patient who at one point received 4.0 mg. daily was finally stabilized on a dosage of 1.25 mg.

One of the younger children received 1.2 mg. of the drug daily, in the elixir, without undue drowsiness. In fact there appeared to be an increased alertness in this as in several of the children.

It is our hope that a more rigidly designed study, one in which the physician has a greater degree of control over medication and environmental factors will follow this study. We believe that our observations have indicated a definite response to the drug in certain cases. We hope to be able to test this preliminary hypothesis by treating a number of children in a hospital setting. We have some questions as to the suitability of comparable control series, since the factors influencing the child's behavior are so varied and so unique, that to find comparable patients seems to us to be a more or less impossible task. We feel that because of the chronicity of the condition, and the slight change which might be expected over a matter of several weeks or even months, that the most accurate test of the drug would be to use the patient as his own control,—that is, to alternate periods of medication and periods without medication. Placebos could be used as an attempt to reduce psychic influences on patients and personnel. The child could be observed and various tests administered after an adequate period of medication, or of control period. The fluctuations of progress and of regression would demonstrate whether or not the drug was actually influencing the condition.

The enthusiasm which we feel must be recognized as being based upon extremely limited changes in the patient's condition. Training and rehabilitation in cerebral palsy is an extremely prolonged, laborious, and relatively unpredictable procedure. It would be unrealistic to expect the drug to change this process remarkably, but we feel that there is some indication that in certain cases reserpine seems to be of definite benefit. It is our hope that continued investigation will result in the development of a greater skill in prescribing and in selecting the most suitable drug.

Although our findings cannot, by any means, be considered conclusive, we believe that our studies suggest a number of conclusions.

1. Reserpine is not effective against the primary neurologic defect in cerebral palsy.

2. The drug has a tranquilizing effect in certain individuals handicapped by cerebral palsy similar to its effect in other states.

3. Because of the above effect the drug is of benefit in two conditions: (a) the child with cerebral palsy having overt psychiatric symptoms; and (b) in relieving tension associated with difficult and frustrating training activities.

4. We believe that reserpine has a definite place as an adjunct to the physical therapies in children handicapped by cerebral palsy, and who in addition have frank psychiatric problems with tension. We believe that the addition of reserpine to the treatment program will in some cases result in a definite increase in benefit observed from the physical therapies.

5. Intensive controlled studies to test the effectiveness of reserpine are indicated. Such tests ideally should be made upon inpatients.

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Discussion (Abstract)

Dr. Leslie B. Hohman, Durham, N. C. First I wish to congratulate Dr. Watkins on the conservatism of his report. My own experience with Serpasil in cerebral palsy is limited to an experiment that is now being carried on at the North Carolina Cerebral Palsy Hospital. All of the children there are receiving Serpasil in a double blind experiment; at least none of the physiotherapists, occupational therapists or the Director of Rehabilitation, knows whether the children are receiving placebos or Serpasil. The Director of Rehabilitation and her co-workers assure me that they have seen no definite change in any of the children which could in any way be regarded as striking.

I communicated with Dr. Winthrop Phelps, one of the outstanding authorities on cerebral palsy, and he informs me that he has tried Serpasil in a considerable number of patients, chiefly with athetosis, and that he finds the drug valuable only in cases in which any kind of excitement increases the involuntary motions. He says further that in the calm type of athetosis he has seen no change.

Dr. Meyer Perlstein, another authority in the field of cerebral palsy, writes that Serpasil is of no value in cerebral palsy but believes that one can be fooled into thinking that it is of value because in some people who get drowsy with the drug there is less hyperactivity.

I would like to call attention to the experiments of Dr. Perlstein when Prostigmin was so highly recommended in cerebral palsy. Dr. Perlstein's experiments showed clearly that any improvement that took place in the child was almost entirely the result of extra interest in the physiotherapist. The final upshot of his study in more than 60 cases was that there was no benefit from administration of the drug but that if the therapist thought the child was getting the drug the child showed improvement, the child might in reality be receiving only a placebo.

I think Dr. Watkins is to be commended for suggesting that the best type of experiment would be using the child himself as a control. Since each case of cerebral palsy is so highly individualized a problem it would undoubtedly take many hundreds of cases to prove anything by a double blind experiment.

Dr. Christopher Morris, Galveston, Tex. I had some experience with cerebral palsy children in New England, but it was ten years ago. More recently, I have served as the psychiatric consultant for the Texas State School for Cerebral Palsy Children here near Houston, but actually have not been in very close contact with large numbers of them for quite some time.

I feel a little bit odd in talking about cerebral palsy children, since I must confess I have had no experience myself with the use of reserpine in them. In reading Dr. Watkins' paper, I was extremely gratified to discover that psychiatrists were becoming interested in cerebral palsy. For a long time the disease was considered the special province of the orthopedist, and anyone else who talked about the subject was thought to be out of bounds, at least I had that experience.

When an author has spent time and energy in preparing a paper, it is reasonable to assume that quite a few ideas have occurred to him of a marginal nature which he has purposely left out of his finished product. I think it would be rather presumptuous for a discussant to add his own ideas since they probably have already occurred to the writer, been weighed by him and have been purposely excluded.

This paper is very obviously the fruit of a lot of hard work and careful preparation, and I personally would first like to express my thanks to Dr. Watkins for his conscientiousness in preparing it. He summarizes by saying he undertook the survey of reserpine and cerebral palsy children to determine whether a subsequent rigidly controlled research project would be justified, and his conclusion is that it would be justified. Apparently in the hands of his group reserpine had a definite tranquilizing effect in children who manifested overt psychiatric symptoms or who manifested tension because of frustrated training activities. I just commented that cerebral palsy used to be the province of orthopedists almost exclusively. Experience has shown, a point that is underlined by the paper, although not brought out perhaps exclusively, that children who have cerebral palsy can be helped more effectively if a team of skilled workers is brought into the picture. The paper mentioned physical therapist, speech therapist, occupational therapist, psy-

chotherapist, school teacher, organic neuropsychiatrist, and, of course, the parent.

We can accept the conclusion that reserpine had a tranquilizing effect on this particular group of children, but let's also remember that that tranquilization probably could not have been adequately utilized unless a skillful professional team was available to capitalize on it. I would like to speculate that perhaps much of the tranquilizing effect was due to the attitudes of the team that used the drug as was due to the reserpine itself.

One further point is, to achieve tranquility is not an end in itself. This was brought out in the paper. We have lots of tranquil patients in the back wards of our state hospitals. Increased tranquility is, of course, a gain only in so far as it serves a purpose, and in this case the purpose was to help these children acquire more effectively coordinated motor skills. At least the impression I got from the paper was that that was one of its areas of greatest usefulness.

Again I would like to say that the acquisition of effective motor skills is also not an end in itself. To be able to dress or feed one's self, or to be able to communicate with others, and walk, is by no means a guarantee of a useful, productive or satisfying life. Many individuals who are intact, neurologically, never do achieve any sort of life that is satisfying either to themselves or to anyone else.

It is recognized that Dr. Watkins, I am sure, had these points in mind and probably purposely omitted mention of them in his paper. Perhaps he considered them so obvious that mention was not needed. My own experience has been that we frequently forget the obvious, and in medicine we often become so confused about a symptomatic gain that we forget that the long-range role is that of a useful and satisfying life in patients to whom we are attempting to offer help.

Dr. Watkins proposes that a research program would better be carried out with inpatients. Our Texas State School for Cerebral Palsy Children, which is an inpatient facility is in my own town of Galveston. I know of no long-range study of reserpine planned at this moment. I am certainly going to alert the director of that school to this paper of Dr. Watkins. I would like to hear in the future whether Dr. Watkins himself is able to set up his proposed project in New Orleans. It would be especially gratifying to hear that the project was a long-range one.

Dr. Frank J. Ayd, Jr., Baltimore, Md. I have just one question I would like to ask. The reason I am so concerned about this is that we hear so much about a drug being or not being effective, with little mention made of the dosage of the drug. So I would like to know what dose was being used in these children, both by Dr. Watkins and Dr. Hohman.

In addition, has it been observed whether these children tolerate these drugs, or this drug, better than adults? I have a feeling, from the children I have worked with, that they have a better tolerance than the child without brain injury. I am interested to know whether you noticed an increase in enuresis, whether children developed Parkinsonism on the dosage you were using, and, finally, whether you have been able to make any correlation between your EEG findings and the results with reserpine. Specifically, I am interested in knowing whether the children with brain injury and having slow-wave activity do better than children with brain injury having fast activity on the EEG.

Dr. Watkins (Closing). I would like to thank the discussants. It is gratifying to know that Dr. Perlstein and Dr. Phelps share some of my conservatism in the reporting on this drug. When Dr. Hohman told me initially of Dr. Perlstein's comment, I thought that he was in disagreement with what I said; when I listened a little more, I learned that we both agree that it is simply a sedative with quieting effect.

Dr. Morris brings up the point that there is no point in tranquility and there is no point in treatment of motor skills unless it is for the benefit of the patient as a whole, and something constructive for the future. I certainly agree with that. I did not go into the total objective of our treatment program, and I did not by any means intend to exclude the use of psychotherapy or psychotherapeutic technics as one of the things we ultimately want to use. We are attempting to set up our program on a long-range basis and to use not only the things that have been mentioned currently, but any other technic we feel will be of benefit to the patient in developing a person who is able to utilize whatever motor skills he does have to the maximum for his own pleasure and benefit.

Answering Dr. Ayd's comment,—the dosages, I think, are considerably higher than we have seen reported in children and than we have used on our adults. The maximum dosage in this series was 4 mg. per day in the 13 year old child. Much higher dosages are being used in adults now but we have not done so routinely in our work. The dosage scale we used was flexible, starting out on a low dosage and increasing doses until we got to a point, where we felt we were getting no further increase in effect; we then started reducing the dosage until we found a dosage that seemed to offer maximum results. The 6 year olds used up to 1.2 mg.

As far as complications are concerned, I did not mention them because we had none of the major complications such as Parkinsonism. We had, of course, some diarrhea which was readily controlled. The one patient with the "asthma" and the erythemaform eruption in one individual I have mentioned, enuresis was not present.

Trichomonal Vaginitis: An Emotionally Conditioned Symptom*

S. FOSTER MOORE, JR., M.D., and JOHN W. SIMPSON, COL., M. C., A.U.S.,† *San Antonio, Tex.*

The authors favor emotional stress as an important factor in the symptomatology of trichomonal vaginitis.

ABOUT TWO YEARS AGO we[1] presented the concept that the organism *Trichomonas vaginalis* is incapable of producing symptoms except in those individuals in whom the vaginal tract is conditioned by emotional disturbances. We said that vaginitis associated with *Trichomonas vaginalis* is not a local disease that can be dealt with satisfactorily simply by eradication of the organism. Continued observation has reinforced this concept. We now want to consider this concept in terms of what is known about trichomonal vaginitis and evaluate its therapeutic implications.

Trichomonas Vaginalis

Although it was first described and associated with abnormal vaginal discharge, by Donne in 1836, the organism *Trichomonas vaginalis* and how it produces vaginitis still is not well understood. Actually, Donne associated the organism with diseases of the cervix rather than the vagina and thought it was gonorrheal in origin. It was not until eighty years later, in 1916, that Hoehne revived interest in the organism by suggesting that it was the etiologic agent of a specific vaginitis. Regarding this there continues to be some controversy.

There are those who hold that a specific vaginitis results entirely from the infestation with *Trichomonas vaginalis*. There are others who suggest that the symptoms result from a symbiotic relationship between the trichomonad and associated bacteria. Also, some believe that the trichomonad is a saprophyte and that its presence is unrelated to the clinical manifestations. However, it would seem that the classic experiments of Trussell[2] have proved beyond any doubt that *Trichomonas vaginalis* is the specific etiologic agent of the vaginitis associated with its presence. Almost by accident, through a combination of persistence and fortunate circumstances, he was able to secure a bacteria-free culture of *Trichomonas vaginalis* in 1940. Subsequently, he inoculated 29 women volunteers with these cultures in amounts containing from 200,000 to 2,000,000 organisms. It is interesting that 20 of these individuals were completely refractory to the inoculation. Of the 9 infected, 7 had mild to severe symptoms, and 2 had no symptoms whatever. In none were the symptoms persistent, and in all the organisms disappeared in a few days. It is important to the discussion of our concept that in none of these 29 presumably healthy individuals was it possible to produce the persistent, chronic, or recurrent vaginitis which is commonly seen clinically.

We believe that *Trichomonas vaginalis* is a *relative pathogen* which thrives and reproduces only in a vaginal tract so conditioned by the emotions as to produce an ideal environment for its growth. That certain conditions must prevail in the vagina for the trichomonad to flourish is an idea which is held by others. In general, these conditions have been thought to be: (1) alterations in vaginal acidity; (2) variations in bacterial flora, especially in a decrease in the lactobacilli; and (3) excesses or deficiencies in estrogen effect. It is doubtful if any of these conditions necessarily predispose to the development of vaginitis. Trussell concluded from his inoculation experiments that vaginal pH well below 5.5 did not prevent successful inoculation, and that symptoms of vaginitis may be produced irrespective of the pre-existing vaginal flora. Trichomonal vaginitis occurs most frequently during the

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nonpregnant reproductive years when the estrogen levels are presumably normal; its incidence is uncommon before puberty and after the menopause, when the levels are low, and during pregnancy, when they are very high.[3]

It is our belief that these conditions *result from* the infestation, for the most part, and do not necessarily predispose to it. It remains to be demonstrated just what chemical or physical change does occur in the vaginal tract which predisposes to the development of trichomonal vaginitis. We have investigated the possibility that altered blood flow through the pelvis, with resulting variations in the vaginal temperature, may be the change which results in the development of such vaginitis. This was suggested by the observations of Duncan and Taylor,[4] who noted temperature changes in the vagina occurring as a result of emotional stimuli. However, we have not been able to substantiate this by the method we have used thus far.

Mode of Transmission

Our lack of knowledge concerning the life cycle of trichomonal vaginitis leaves a broad gap having to do with its mode of transmission. The organism lives in the vaginal tract and may or may not produce symptoms. It does not invade the vaginal epithelium, and it has not been proved that it ever extends to or beyond the cervical canal. Its occasional presence in the urine indicates that it may gain access to the bladder, but there is no reason to believe that it ever does well there, or that it produces cystitis.[3] Urethral contaminations are rather common, however, and urethritis frequently is an accompanying symptom.

No free-living form of the organism has been discovered.[5] It is found only in the genitourinary tract and thrives nowhere except in the vagina. Actually, all we know about its life history is that it reproduces by binary fission. It does not produce encysted forms as was once thought, but in response to noxious stimuli undergoes a curling and shrinking which causes the organism to resemble a cyst. However, instead of being a resistant form, these "pseudocysts" soon decompose and disappear. Indeed, we have no knowledge of how the organism gains access to the vagina or from where it comes. That it may exist outside the vagina in an air-borne "spore" form is a possibility. Certainly, it seems to occur "spontaneously" in the vagina without any known source of infection.

It is well established that vaginal infection with *Trichomonas vaginalis* does not occur as a result of fecal contamination,[6,7] a belief which was prevalent some years ago. It is known that there are only two other trichomonads parasitic to man: namely, *Trichomonas tenax* which inhabits the buccal cavity, and *Trichomonas hominis* which is found in the intestinal tract. These have been demonstrated as being morphologically and physiologically separate and distinct species from each other and from *Trichomonas vaginalis*. Each is suited only to its own environment and is incapable of surviving in the environment of the others. With this knowledge so well established it is unrealistic to associate these organisms with any type of vaginitis.

The role of the male in the transmission of the trichomonad must be considered. We believe that transmission by the male is of little if any importance as a source of the infection, and there is much evidence to support this contention. In the first place, the environment afforded by the male genitourinary tract is entirely unsuited to the trichomonad. In the second place, if trichomonads were able to survive and reproduce in the male genital tract to an extent which would be necessary for the male to serve as a focus of reinfection, it seems reasonable that symptoms would be produced in the properly conditioned male. It may be a mere contaminant. Finally, avoidance of sexual contact or the use of condoms does not prevent recurrences of vaginitis in susceptible individuals.

Treatment

In our previous presentation of this subject we suggested a two-fold approach to the treatment of trichomonal vaginitis. This consisted of: (1) the use of local agents for the eradication of the trichomonads, and (2) measures intended to improve the patient's emotional health and general well-being. Additional experience gained in this technic has made it seem worthwhile to present our methods in more detail.

Local Agents. Hundreds of simple, inexpensive, and safe chemical agents are capable of inactivating the trichomonad in the vagina.[8] Most of these have been tried clin-

ically with varying degrees of success. Dozens of preparations have been promoted almost continuously which are said to be effective in the control or cure of trichomonal vaginitis. This emphasizes the relative ineffectiveness of all these drugs and the highly profitable potential market which exists for any really successful agent. At best, the majority of these provide symptomatic relief when used according to the manufacturer's directions, and they do not harm the patient. Claims as to "cures" are highly unreliable and are based on the finding of organism-free secretion in the vagina for varying numbers of months following treatment. The assumption is that if all the organisms can be eradicated from the vagina and adjacent structures cure will be effected. Actually, it is probable that all the organisms are destroyed after any series of several treatments. The problem is the recurrence after the cessation of treatment. It is unlikely that any agent used locally will ever prevent this.

We have used practically all of the agents which have been recommended for the treatment of trichomonal vaginitis and have not been impressed with the great superiority of any one agent over another. It is our belief that to be considered acceptable a preparation should fulfill the following requirements listed in order of importance: (1) be harmless to the patient, both locally and systemically; (2) provide prompt relief of local symptoms; (3) its application be acceptable to the patient; and (4) it be relatively inexpensive.

There are a number of preparations which fulfill these requirements. Our own preference is for a powder which is blown into the vagina at each office visit. In the initial phase of treatment the patient is not given any medication for self-administration. Complete relief of local symptoms can be obtained in a few hours by means of this treatment, and the patient will remain comfortable for three or four days, when we will want to see her again anyway. We believe that too much local medication is harmful and serves to emphasize the symptoms which we are striving to minimize. Usually our patients receive no more than three or four treatments for any one recurrence. Later in the course of treatment we may prescribe a medication which the patient can use herself. For this we generally use a vaginal tablet or suppository.

Local treatment of the vagina is not essential to the management of trichomonal vaginitis. We have successfully treated a number of patients without any vaginal medication. However, in most instances we have found it expedient to employ local measures. This gives the patient prompt relief of her symptoms and thereby aids in establishing satisfactory rapport. Among a group of selected patients for whom we chose not to use vaginal medication, symptoms of discharge and itching were not relieved immediately, and the management of the patient was made more difficult by their persistence. As long as these complaints continued it was almost impossible to turn the patient's attention to her general condition. In several we did not persist and turned to local treatment. However, in one patient complaints pertaining to the vaginal condition were never mentioned after her initial visit, and she has had an indefinite remission without ever having had any local treatment. This seems significant since spontaneous remission of trichomonal vaginitis is quite uncommon. In some others topical application of anesthetic creams allayed local discomfort at the outset of treatment. Many patients with trichomonal vaginitis are greatly benefited by sedation, and phenobarbital constitutes an important item in therapy. Initially this is most important in relieving the emotional tension and makes the patient generally more comfortable. Many of our patients with trichomonal vaginitis have real physical fatigue which aggravates their condition. We prescribe additional rest for these individuals even if it may necessitate giving up a job outside the home or securing help with household duties. Furthermore, we make an attempt to relieve accompanying symptoms which are not referable to the vaginitis. Abstaining from sexual intercourse seems to aid in recovery from the acute phase of trichomonal vaginitis. For this reason, we advise the patient to have no sexual contact during the first week or so of treatment.

General Measure. Increasingly we are more impressed with the results in trichomonal vaginitis obtained by treating the whole patient. In fact, it seems that this is indispensable to the proper management of the condition. This approach has been very satisfactory to the patient and has been a source of much personal gratification to us. As we have

said previously, we have been able to avoid the frustration that the condition had caused us as well as the patient.

The direct psychiatric approach to the treatment of trichomonal vaginitis by the nonpsychiatrist is not unlike the management of other psychosomatic disease. This consists of: (1) establishment of rapport, (2) relief of symptoms, (3) allowing the patient adequate verbalization, and (4) reassurance.

In establishing the proper relationship with the patient, the initial contact is extremely important. This is especially true if the individual has been plagued with the condition for some time. Often she has been to several other physicians and has had much treatment with no lasting relief. She is apt to begin the discussion of her complaints by describing the various treatments she has had and in so doing clearly indicates the passive hostility she has toward those who have attended her. She may be greatly discouraged by the failure of her previous treatment and, in fact, may have come to believe the condition incurable. She should be allowed to tell her story in her own way with a minimum of interrupting questions. If she cares to include in her history a description of her emotions and attitudes, she is encouraged to do so, but probing in this direction should be avoided. Usually it is necessary to inquire about the patient's activities because this information is seldom volunteered, and because it is important to a proper evaluation of her emotional background. A careful and complete gynecologic examination is a further means of gaining the patient's confidence. Hasty inspection of the vulva and a quick speculum examination implies to the patient a lack of sufficient interest on the part of the examiner.

Just how far the gynecologist should proceed with psychotherapy will depend upon his interest and his ability. At least he can listen and encourage the patient to talk. Her attention should be directed away from her vaginitis, and a few questions usually will bring out a great deal about her background. It is remarkable how many of these patients are confronted with really stressful life situations, and verbalization is invaluable to them. In others the life situation constitutes a less real but no less realistic threat. Marital difficulties are common and often are associated with frigidity. If the patient wants to discuss her sexual difficulties, she should be allowed to do so, but in most cases the examiner would be unwise to conclude that this is the basis of the emotional stress, and especially he should not indicate this opinion to the patient. Usually at each succeeding visit the patient will be less inclined to dwell upon her vaginitis. Eventually she will be discussing her life situation or her attitudes instead. When this occurs, progress will have been made in relieving her vaginitis and in creating a feeling of well-being and tranquility which will tend to prevent its recurrence.

We do not hesitate to reassure the patient as to eventual cure. We feel optimistic toward the ultimate outcome in almost every case, and we allow this feeling to be transferred to the patient. Careful explanation concerning the nature of the symptom, the organism which is directly responsible for it, the limited nature of the symptomatology, and the probable outcome of the condition is generally comforting to the patient. Such reassurance tends to lessen the apprehension which some of these individuals feel when they are first seen. A pessimistic attitude on the part of the physician would serve to increase the patient's stress and delay her recovery.

Results of Treatment

A great majority of our patients are successfully managed by the method we have outlined. Almost all are relieved of their vaginal symptoms within a few hours after their initial treatment. In addition, most of them show an improved attitude toward their symptoms and report an increased sense of well-being. Recurrences do occur, even while we are seeing the patient regularly, but these are not common. The greatest number of patients will have prolonged remissions, which may be looked upon as cures, after no more than two or three months of treatment. Few patients reject the idea that the emotions are important in the production of their symptoms, and most are relieved to have an explanation offered them. Patients who do not respond to the superficial psychotherapy which we employ are encouraged to seek treatment by a psychiatrist, but relatively few need this. However, in such cases, results usually have been good when we have treated them in conjunction with a psychiatrist.

We have not reported our results in terms

of percentage of patients free of symptoms and organisms for an arbitrary number of months because we believe that such a table would be valueless. In the first place, our patients do not represent a good cross-section sampling. Many of them represent chronic resistant cases and patients who have been treated over a period of months or years, and it is unusual to see a really "new" case. Secondly, it is extremely difficult to determine what constitutes a "cure." There is no acceptable standard by which results can be measured. Finally, we think that results accrue to the patient in terms of improved emotional health which cannot be evaluated in any tangible manner.

Summary

The concept that trichomonal vaginitis is incapable of producing symptoms except in a vaginal tract conditioned by emotional disturbances is again presented.

The relative pathogenicity of trichomonal vaginitis is discussed.

Our plan of treatment is outlined.

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Discussion (Abstract)

Dr. Robert N. Creadick, Durham, N. C. Drs. Moore and Simpson are to be complimented for their courage in presenting this bold concept. The evidence has been before us for many years, yet no one has *dared* in the past to be so specific. In the following discussion, I would like not only to commend them, but also to add further evidence in support of their thesis. For me, it is a dramatic moment when gynecologists can get together and make a concerted effort to understand the bases of emotional symptomatology. Most of the literature concerning the following disorders contains a short paragraph in this fashion: "Several of our patients were so neurotic they did not respond to treatment," or "All of us are aware that psychological difficulties, and emotional overlay, are present." Thus various authors depart from honest management of such disorders as vaginitis, vulvitis, dysmenorrhea, frigidity, and menopause. In all of these conditions the absence of very much in the way of anatomic findings is quite evident, and the degree of complaint has always seemed a little distorted in relation to the visible or palpable pathology.

The authors of this paper have presented trichomonas as a *relative pathogen*. I might even be so bold as to suggest that by itself it never produces any disease process!

The Evidence. 1. Trichomonads can never be made to fulfill Koch's five postulates.

2. The trichomonal vaginitis cannot be transmitted in human volunteers from vaginia to vagina without certain specific prerequisites.

3. The sudden appearance and disappearance of the symptom could not possibly follow ordinary pathogenesis by any one organism,—for example, the patient arising at 7:00 a.m. feeling perfectly well until 7:30 a.m. when *sudden*, intense itching appeared.

4. The organism is present in so many of our patients without any symptoms whatsoever.

5. The old-fashioned idea that this was a contamination from the rectum can no longer be held, since *T. hominis, T. vaginalis, T. tenax* (buccalis) are separate and distinct. They are even "area-specific" like gonorrhea. A few urologists still feel that the existence in the urine might be evidence of trichomonas as an agent in cystitis. We have always felt this was a contaminant from the urethra.

6. In patients with Type I vaginal smear, which shows a low pH and is entirely filled with normal Doderlein bacilli, the organism will not "take" when transplanted. The presence of blood or excessive cervical mucus would, of course, raise this pH.

7. It is the general opinion in our clinic that the symptoms for which the trichomonas has been blamed arise from anaerobic organisms associated with the presence of trichomonas either symbiotically or by accident.

Treatment. The authors have delineated the vital points in management of their patients. I would like to add that these should apply to *all* patients, not just those with trichomonal vaginitis. They have outlined without heavy psychiatric verbiage a method of listening, examining carefully, and reassuring. It might be wise to go one step further if the physician's interest and serious attention can be maintained. He must gradually present the patient with fairly tangible chronologic evidence that the symptom is based on stressful situations, or emotional upheavals. This necessitates explanation such as the following:

1. There is no bacteriologic disease that itches intensely *only* at night, or *only* at 5:00 p.m. (when the husband walks in the front door).

2. The worst spells occurring on Saturdays, Sundays, or holidays is still further evidence of disturbing influences, often from the husband's peregrinations, or the horrendous influx of droves of relatives.

3. Comparison of distressing days containing disturbing events and severe symptoms with the good days when the patient feels perfectly well, will help.

4. Comparison of testing periods, like a vacation, or even a long weekend, away from husband, children,

Mamma, etc., will lend evidence to the degree of situational, as well as personal, reaction.

5. In a long history of vaginitis, there may be gaps of several months when the patient did not have itching. The evidence surrounding these times is most productive in providing answers for the physician and patient seeking basic causes of the symptom.

6. A discharge from the vagina may have special meaning to the patient—this must be explored. Many patients, and quite a few doctors, interpret any discharge from genital areas as venereal disease. It might be worth mentioning that of all the various effluvia from the vaginal tract, only one might be associated with venereal disease, and it certainly does not itch! Nor does it have any odor; nor is it very profuse.

7. The symptom of itching is a complete chapter in itself and represents a multitude of human frailities such as anger, excitement, embarrassment, frustration, sexual tension, and even occasionally pleasurable stimulation.

8. The longer the symptom persists, or the more often it recurs,—whether or not it was initiated by trichomonas, monilia, poison sumac, or chemical irritant (like over-treatment), the less likely the physician is to effect a cure. In fact, he cannot even ameliorate the condition except very temporarily without adequate psychotherapy. A pale, but distinct light has broken upon the gynecologic horizon. Several clinics have now instituted efforts for better liaison with psychiatric departments. Many, like us, have joint conferences weekly. More and more recognition is given to the emotional needs of the patient. Neuropsychiatric specialists are coming out of their ivory towers and gynecologists are becoming more attentive, and less and less resentful of "the nerve doctor." It has been most rewarding for me to find physicians interested in "comprehensive medicine." This implies that we can again treat the patient as a human being, not as a uterus or "a case."

Again, I want to congratulate Dr. Moore, and his coauthor, Dr. Simpson, for their intellectually honest approach, and for the privilege of discussing this paper.

Dr. Simpson. Thank you, Dr. Creadick, for your very complimentary discussion. It was with considerable misgiving that we first presented this concept, but we have been pleasantly surprised to find many gynecologists in agreement with us. True, many who agree have agreed only after thinking it over for some time.

Perhaps several of you here are wondering about the application of this concept to the study of vaginal moniliasis. We believe that emotional conditioning of the vaginal tract plays an important role in this symptom complex, too. As you know, *Candida albicans* can be cultured from almost every woman's vagina as well as from nearly anywhere else. In fact, when making cultures of vaginal secretions for organisms other than *Candida albicans* a suppressor of Candida must be added to prevent it from overwhelming the other organisms for which we are searching. Why, then, do not all these women develop symptomatic vaginal moniliasis? It is probable that some conditioning or alteration of the physiology of the vaginal tube must be present to enhance the development of the moniliasis. This could be, and we believe often is, a conditioning by the effects of emotional crises or fatigue. Because there are several differences in the basic conditions under which symptomatic vaginal trichomoniasis and symptomatic vaginal moniliasis develop, we chose to limit our presentation to trichomoniasis until we have made further investigations.

We do know that vaginal temperature is greatly influenced by stress, but no reliable basic data on vaginal temperatures are available. We have underway a study of this phase of the basic physiology involved and hope to have reliable data within a year.

Dr. K. J. Karnaky, Houston, Tex. Dr. Moore and Dr. Simpson have brought to our attention the emotional aspect of trichomonal vaginitis. There is an emotional phase to almost all diseases.

Dr. Moore suggested the vaginal temperature was higher in trichomonal cases than in non-trichomonal ones. We used an electronic temperature instrument in trying to prove this but no elevation of the vaginal temperature was found in these trichomonal infected vaginas, unless there was an acute vaginitis. All acute cases of vaginitis gave the same temperature readings regardless of the cause.

We have inoculated trichomonads into more than 500 vaginas and have proved Koch's postulates. I have placed leukorrhea due to trichomonas that burned on various parts of a patient's body and it burned her even though she did not know that I was placing the secretion on these parts.

We have been using a chemical which blocks pain centrally (medial lobe of the thalmus). In trichomonal itching and burning this drug (Dipo, the solution; Dipain, the rectal suppository) stops the itching and burning of nonpsychogenic origin but not that of psychogenic origin. It is safe and can be given in large amounts with no side reactions in over 300 patients. It can help to differentiate between true or functional itching and burning of the perineum.

I cannot agree that the male is not important in trichomonal vaginitis. I have stopped over 300 stubborn cases from recurring by having the wife insert 3 to 6 Baculin tablets following coitus. This destroys the re-inoculated trichomonads from the male. I recommend this routine treatment following coitus rather than douches or condoms with few exceptions.

I have examined over the years over 500 children with vulvovaginitis and have seen only a few cases of trichomonal vaginitis and these children had been raped or had had coitus. The male is important in recurrences of trichomonal vaginitis. I wrote years ago that trichomonal vaginitis was a partial venereal disease. That statement still holds.

Again, Drs. Moore and Simpson have brought to our attention the emotional angle of trichomonal vaginitis. In any disease the physician should study the entire patient, both mentally and physically. Too many of my patients think their husband has given them a Neisserian infection and that he has been unfaithful. This causes great emotional upset and makes the itching and burning worse and many will scratch the perineum even to injure the labia. Trichomonal vaginitis is becoming more of an emotional condition because patients not being cured of infestation, begin to think they have cancer. We are still trying to find a way to destroy the trichomonads in the male but without success. The organism dies out in the male within

3 months if he is not reinfected. The wife destroys inoculated trichomonads following coitus by the use of Baculin tablets or blowing in of Trimonil powders.

Dr. O. J. Potthast, San Antonio, Tex. This discussion reminds me of Saxe's poem of satire on theologic disputes telling of six men of Indostan who went to see the elephant (though all of them were blind). One felt the tail and said it was like a rope, one the trunk and said it was like a serpent, one felt the side and thought it was like a wall, and so forth. And so these men "disputed long and loud," though each being partly in the right and all were in the wrong.

The essayists and the discussers each have been considering one part. But in our treatment we have to consider the patient as a whole, both physical and mental.

Having been in practice forty years, treating trichomonas about thirty-five years and never having seen a chronic condition of any kind which did not have periods of remission I believe I can add my bit.

I do not go along with the idea that we do not have infection and reinfection from the rectum. I am convinced that such infection of the vagina is a fact, although I am aware of the experimental work supposedly disproving this. If this were not so we would not get the results which we obtain by giving antitrichomonads by mouth to clear the intestinal tract in addition to our local treatments. Personally, for years, I have given two courses of carbarsone, a course of 20 capsules, one three times a day, and repeated after 10 days.

In addition to treating the vagina do not forget to treat the Skene's glands, using a lachrymal duct canula for irrigating these glands. Also, to my satisfaction it has been proved again and again that reinfestation from the husband can keep up the trouble, although I am convinced (at least in my practice) that men comparatively seldom become infected although the mate must have had trichomonad infection for years. In one case I got about a twenty year history of disease and still the husband did not have trichomonads. The male anterior urethra apparently is resistant to it. But once it gets into the posterior urethra it is most difficult to get out. I am not yet convinced that Dr. Karnaky is right, that it will die out in six months unless reinfected. He and I have been arguing and discussing trichomonas for many years.

The psychic condition, of course, helps in the remission and easing of all kinds of illness. This is an absolute fact which we all know. Positive assurance to the patient that the condition is not serious is a great aid.

I think this paper by Drs. Moore and Simpson is very important and enlightening, but it is just one step in the treatment of this condition.

Dr. Moore (Closing). I thank all of these gentlemen for this interesting discussion of our presentation. We expected to elicit a certain amount of controversy. As a matter of fact, the first time we presented this idea I had even more misgivings than I did this morning.

In response to Dr. Creadick's observation, that these patients may need some convincing as to the emotional nature of the symptoms, let me say that his technic is an excellent one in cases where the patient seems to be unable to put together the emotional symptoms and the vaginitis. The interesting thing to us has been that very few patients have the slightest hesitancy in accepting the notion that recurrences of vaginitis follow immediately situations of emotional stress and so forth.

I have a very high regard for Dr. Karnaky's knowledge of trichomonal vaginitis and I realize that he has done a great deal of work along this line, but I think I might say that his approach to the problem has simply been somewhat different from ours. I am going to wait until he finds the ideal local agent. In the meantime, I am going to go on treating my patients in the manner in which we are handling them at the present time.

Anesthesia for Pediatric Neurosurgery*

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In neurosurgical procedures in young children, the details of anesthesia and of preoperative and postoperative care are of double importance.

THE VULNERABILITY OF CHILDREN to physiologic sequelae of anesthesia and neurosurgery imposes upon the anesthetist and operator unique responsibilities. The margin of safety is narrow, and relatively minor errors in judgment result in magnified effects on the patient. Mutual understanding between neurosurgeon and anesthesiologist of the conditions under which each must work is mandatory to their successful collaboration. This relationship is dynamic and should continue into the postoperative period.

The following conditions should prevail in the anesthetic management of children undergoing neurosurgical procedures: (1) The patient should arrive in the operating suite without undue depression from premedicant drugs. (2) Induction should be smooth, unhurried and free from bouts of breath-holding and laryngospasm, and with as rapid transition from first to third stage as possible. (3) The airway should be free of resistance at all times. (4) Anesthesia below first plane of stage three should be avoided as it is rarely necessary. (5) Embarrassment of respiratory or circulatory functions from malposition should never be tolerated. (6) Intracranial pressure should not rise above the preoperative level. (7) The operative field should be free from encroachment by the anesthetist and his equipment. (8) Water, electrolyte and blood replacement should proceed according to the estimated loss. (9) Emergence following discontinuance of the anesthetic agent should be rapid and not delayed by "hangover" effects from hypodermically administered depressants.

These are factors which are within the control of the anesthesiologist, although their attainment is often difficult.

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Preoperative Medication

Morphine, meperidine and their derivatives are avoided in operations within the skull, but may be given to older children when otherwise indicated. To suppress secretions and provide some degree of amnesia, scopolamine is the drug of choice. The dose varies from 0.08 mg. in infants to 0.30 mg. in older children. Larger doses may be given safely[1] but have not been found necessary. Atropine and barbiturates tend to mask vital warning signs of dangerous hypoxia.[2] In emergencies intravenous premedication is given 10 to 20 minutes prior to induction. Subcutaneous administration should be done 60 to 90 minutes preoperatively.

Choice of Agent, Induction and Maintenance

With a few exceptions as noted in the following text, general inhalation anesthesia is preferred. The choice of agent should be left to the anesthesiologist who is to administer it. He alone knows those which are safest in his hands. If there should be apprehension that one agent may effect intracranial pressure more than another, one may rely on recent studies[3] which have shown that no agent *per se*, with the exception of tribromethanol, specifically increases pressure. The technic by which they are administered is the critical factor governing their use.

Irrespective of whichever agent is used, there should be no undue haste during induction. Sudden high concentrations stimulate secretions and laryngeal reflexes. Nitrous oxide, cyclopropane and open drop ether can all be used successfully for induction. Healthy older children may be induced with sodium thiopental, but in the presence of increased intracranial pressure it is used only to the point of quieting a disturbed child. Endotracheal intubation is considered mandatory in all operations in or about the skull and when the prone position is used. While in-

tubation may not be necessary in every case there is no contraindication to its use. The mere presence of an endotracheal tube is not a guarantee of a free airway. It must be attended by constant observation to avoid kinking, intubation of a bronchus, or obstruction by mucus. Closed system anesthesia has not been used in infants, and it is avoided in all children for intracranial procedures. Open, semiclosed or nonrebreathing technics are preferred if the flow of gases is substantially greater than the estimated minute volume of the patient. Ether is our principal maintenance agent as it does not depress respiration in lighter planes and has excellent analgesic properties.

Position

The neurovascular, respiratory and circulatory effects of extreme positions on the operating table have been studied previously.[4,5] In general, the following criteria are followed: (1) No part of the body should be acutely flexed. (2) Pressure is avoided over major nerve or vascular supplies. (3) Venous return from the head is not obstructed. (4) No restriction is placed on the movement of the diaphragm and pressure on the thorax is limited only by the child's own weight. When the prone position is used, parallel longitudinal supports between the clavicles and iliac crests allow freer expansion of the rib cage and diaphragm. (5) If sitting or extreme head-up tilt positions are necessary, the legs should be either elevated or wrapped to minimize the pooling of blood.

Effects of Increased Intracranial Pressure

One of the most constant problems facing the anesthesiologist and neurosurgeon is increased intracranial pressure. Occasionally ventricular tap prior to induction of anesthesia will facilitate management. If pressure is high the respiratory and vasomotor centers may be affected, and the slightest further increase may prevent ultimate recovery. The following factors tend to raise intracranial pressure: (1) hypoxia, (2) hypercarbia, (3) resistance to breathing, (4) positive pressure respiration, (5) reflex coughing, and (6) restriction of venous return from the head. All are amenable to some degree to control by the anesthesiologist. Premedication, induction, airway control and positioning, which have already been mentioned, may each in its own way affect intracranial pressure. By using ether in light planes the need for positive pressure respiration will be minimized. Coughing on an endotracheal tube can be dangerous at any time. The use of topical anesthesia is usually not necessary if close attention is paid to keeping the patient in surgical anesthesia and avoiding movement of the tube with respect to the larynx and trachea.

Maintenance of Water, Electrolyte and Blood Balance

Several factors constantly tend to promote water depletion. Fluids and food have been withheld six hours or more before surgery. Vomiting often has accompanied intracranial tension tending to upset electrolyte balance. The need for water, electrolytes or blood should be anticipated, and reliable cannulation of a vein by needle or catheter should be done before the operation is begun. Blood loss during neurosurgical procedures is often difficult to estimate accurately. Not only is a large amount taken away with saline irrigation, but drapes and sponges contain varying amounts. The total blood volume of infants up to one year is between 500 and 1,000 cc. A 50 to 100 cc. loss is hardly noticeable on drapes, sponges and in the suction bottle, but represents 10 to 20 per cent of the infant's total blood volume. Blood should be replaced as it is lost.

The anesthesiologist has partial control over blood loss by his ability to prevent respiratory depression and accumulation of carbon dioxide. Several factors tending to increase blood loss are: (1) febrile conditions; (2) arterial hypertension; (3) incompatible blood transfusion; (4) intrinsic disease which may disturb clotting or bleeding time; (5) excessive accumulation of carbon dioxide; and (6) venous hypertension.

Fever causes increased metabolism and vasodilatation. The thalamic center which regulates temperature is frequently affected by disease of the central nervous system. Insofar as the anesthesiologist is able to prevent aggravation of pre-existing cerebral hypertension, this factor affecting blood loss can be controlled. Many patients who come to surgery have arterial hypertension. High intracranial pressure can cause a further rise in

blood pressure. Arterial bleeding is thus increased in the operative field.

The transfusion of incompatible blood with subsequent hemolysis results in capillary oozing that is often extremely difficult to control. Hemophilia and the purpuras, although relatively rare, should be ruled out before neurosurgical procedures are undertaken.

Excessive accumulation of carbon dioxide can result from several conditions which may develop before or during surgery. Carbon dioxide has two actions on the vascular system, both of which contribute to excessive bleeding. First, it has a direct peripheral action which causes capillary dilatation. Second, by its action on the vasomotor center it causes arteriolar constriction and a rise in blood pressure. The following factors contribute to a rise in carbon dioxide tension in the blood: (1) malposition; (2) obstructed airway; (3) heavy premedication; (4) deep anesthesia; (5) curariform drugs; (6) inefficient absorption of carbon dioxide, or rebreathing of exhaled air; and (7) venous hypertension. Each of the first five factors act by reducing pulmonary ventilation. Inefficient absorption of carbon dioxide and rebreathing increase the carbon dioxide content of the inhaled atmosphere. Venous stasis can be generalized due to cardiac failure, or it can be local due to dependent position or obstruction to venous return.

In order to better reach objectives set forth in the preceding paragraphs, a study of 500 consecutive administrations of anesthetics to neurosurgical patients below the age of 14 has been made. The operations are classified and the mortality under 24 hours is summarized in table 1.

The diagnostic procedure of pneumoencephalogram or ventriculogram was performed 141 times. Open system ether by the "Flagg" endotracheal or by open drop technic was used in the majority of instances. Sodium thiopental, used often earlier in the series for children of all ages has lately been used less frequently. In light thiopental narcosis laryngospasm occurred too often, and if reflexes were depressed by more drug, respiratory depression was too severe. Circulatory distress was a frequent complication in this group. Many of the infants and very young children develop a waxy appearance shortly after the injection of air into the subarachnoid space. Where respiratory obstruction is not a factor, this distress does not seem to be related to agent or anesthetic technic used. There was one death in this group which occurred during the operation. Eighty cubic centimeters of air were injected into the subarachnoid space of this nine month old child in a period of less than 10 minutes. The pulse rate increased from 140 to 180 per minute, and as the last 10 cc. were injected, the patient gasped and no pulse could be felt. Postmortem examination revealed massive pulmonary air embolism with air in the right ventricle and the coronary arteries. The choroid plexuses of the two lateral and the third and fourth ventricles consists of very vascular processes of pia mater. It is possible that air absorption occurred by this route. Another possibility is the injection of air directly into the anterior extradural space which contains a plexus of thin walled veins. Air is probably absorbed more frequently than we realize in sublethal doses, accounting possibly for the occurrence of many instances of circulatory distress.

TABLE 1

Operation	*Procedures*	*Per cent of total*	*Deaths under 24 hours*
Pneumoencephalography	141	28.2	1
Peritoneal and cisternal shunts	117	23.4	3
Craniotomy	101	20.2	7
Burr holes	77	15.4	5
Repair of meningocele and encephalocele	33	6.6	0
Arteriography	18	3.6	0
Laminectomy	13	2.6	0

Peritoneal and cisternal shunting operations were performed 117 times. With the exception of a few lumbar peritoneal revisions, these children were intubated and maintained by an open or semiclosed technic. There were three deaths in the 24 hour period following surgery. At least one of these was due to failure to replace blood lost during surgery. Blood replacement, inadequate in amount and too late, was a factor in the other two deaths.

There were 101 operations for craniotomy or major plastic procedures on the skull. Here especially close attention to principles heretofore outlined is needed to prevent undue bulging of the brain outside the open dura. Open system endotracheal ether is again our

choice on older children, and semiclosed systems are used on infants and the very young. Seven of these patients died within 24 hours. One occurred during operation on the medulla approached directly through the fourth ventricle. The others were due mainly to cerebral edema or pressure on the brain stem. However, blood replacement was considered adequate by the anesthesiologist in only two of these.

Operations for relief of subdural collections of blood or fluid and for acute intracranial injury accounted for 77 procedures. There were 6 deaths. Anesthetic management in many of these cases involves delicate questions of judgment. Often the patients are unconscious on admission. Establishment of a clear unobstructed airway takes precedence. This really needs to be done in the ambulance or emergency room during a most critical phase of management, but persons untrained in the art of management of an airway are usually in charge of the patient at this time. If hypoxia due to respiratory obstruction is allowed to persist, the effects of head injury are compounded, and any chance for ultimate recovery reduced. The administration of an anesthetic agent to an unconscious patient without reflexes is hazardous. This type patient should be intubated and have a thorough tracheobronchial toilet. On occasion, following removal of a subdural hematoma, a patient may regain consciousness. Then the need for an anesthetic arises and should be given according to the response of the patient.

Repair of meningocele or encephalocele accounted for 33 procedures in this series. There were three deaths. One of these, a nasal encephalocele, followed periods of severe postoperative respiratory obstruction. This was an eight hour procedure on a three year old child.

Cerebral arteriography was done 18 times. Endotracheal ether was used most frequently. Injection of Diodrast into the carotid arteries is often attended by elevations of pulse rate and blood pressure and by ipsilateral dilatation of the pupil. If barbiturate hypnosis is used without supplemental analgesia, movement of the head may occur as the dye is injected and spoil the radiographs. Extravasation of dye into the neck can be sufficient to cause visible deviation of the trachea and these patients should be carefully observed after extubation in order to be sure there is no obstruction to air flow.

Summary

A review of 500 neurosurgical anesthetic procedures in children has been made. Certain principles in the anesthetic management have been outlined. Adherence to these principles, we believe, will aid materially in the prevention of both surgical and anesthetic complications arising and following surgery.

Discussion (Abstract)

Dr. D. A. Davis, Chapel Hill, N. C. It would be rather presumptive to try to add anything to the principles outlined here for they are simply the principles of good inhalation anesthesia. Certainly the neurosurgical patient, and particularly the infant or small child, deserves the utmost attention of the anesthetist. In these small children any little thing which goes wrong may jeopardize the chances of success of the operation.

It is most important to take one's time during the induction period and in the preparation of these patients for operation. Many times undue haste may precipitate an avoidable crisis, and often the combined efforts of two anesthetists are necessary.

Recently we have been most impressed by the marked fluctuations in spinal fluid pressure which can accompany hypoxia or carbon dioxide excess or both. Although the effects of increased intracranial pressure may be produced by either hypoxia or carbon dioxide excess in a relatively short time, when the carbon dioxide excess is corrected the intracranial pressure falls back to normal quite rapidly. But if an experimental animal is made hypoxic for only a brief period, the intracranial pressure tends to stay up for a considerable period of time. This fact was brought out in the very nice studies on humans of Woodhall, Stephen, and others at Duke University.

I would like to encourage the practice of cancellation of neurosurgical cases if everything is not all right during induction. Too often there is a tendency to feel that the operation must proceed even after a stormy induction. Many of these cases will keep and one can try again on another day.

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Evaluation of the Patient Having Cirrhosis as a Surgical Risk*

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At the present time with surgical technics available with which to attack the complications of portal cirrhosis, evaluations such as this are important aids in the decision to operate.

FOR MANY YEARS the patient with cirrhosis has been considered a poor operative risk. Reports in the older literature noted mortality rates of 30 to 50 per cent following relatively simple procedures such as splenectomy and omentopexy in cirrhotic patients.[1,2] As a result, physicians have been reluctant to advise surgery for patients with this condition.

More recently, it has been noted that patients with unsuspected extensive liver damage often tolerate major surgery well. In addition, an increasing number of patients with cirrhosis and portal hypertension have successfully undergone a considerable amount of surgical trauma during procedures to establish venous shunts. In the past decade improved medical management of both the acute and the chronic phase of hepatitis has induced remissons in a higher percentage of patients with badly damaged livers. Because such patients now live longer, many ultimately develop unrelated disorders which require elective or emergency surgery. Other cirrhotic patients with portal hypertension face the prospect of an untimely death from hemorrhage unless surgical intervention is attempted. In view of the demonstrable ability of the liver to regenerate under proper conditions, as well as the obvious advantages of the increased availability of blood for transfusions and antibiotics for the control of infection, improvements in anesthesia, and better understanding of fluid and electrolyte balance, a re-evaluation of our concepts concerning the ability of these patients to withstand major surgery seems in order.

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Material

Studies were made on a group of 52 cirrhotic patients, 30 males and 22 females, who underwent surgery. Three were children, aged 18 months, 9 years, and 13 years; the remaining patients ranged in age from 18 to 69 years, with a mean age of 43.5 years. In 21 patients the diagnosis of cirrhosis was not suspected at the time of the first operation. In the remaining 31 patients, the diagnosis was made preoperatively. Additional major diseases were present in 35 of these patients. A total of 72 major operative procedures were done, 58 at the North Carolina Baptist Hospital.

The patients were divided into three groups. Group I consisted of 9 patients who expired within 30 days after operation. Group II was made up of 11 patients who recovered from the operation but died within two years after surgical treatment. Group III consisted of 32 patients still alive at the time of this study (an average of 39.1 months following surgery).

Group I. The diagnosis of cirrhosis was made preoperatively in only 5 of the 9 patients who expired in the immediate postoperative period. The various preoperative diagnoses, major complicating diseases, operative procedures, and causes of death are noted in tables 1 and 2. Seven of the 9 patients in Group I gave a past history of jaundice, and 6 had a history of ascites. At the time of operation, all 9 patients had ascites and 8 were jaundiced. Five had splenic enlargement, and the liver was palpable in 3. Four patients received morphine before or after operation. Six were given antibiotics at some time during the pre- or postoperative period.

The cause of death in every instance was hepatic insufficiency. Renal insufficiency was

also present in one patient, and hemorrhage was a contributory factor in another.

Group II. The diagnosis of cirrhosis was established preoperatively in only 2 of 11 patients who survived the postoperative period but expired within two years following surgery. Five patients had a past history of jaundice, and 5 of ascites; at the time of operation 3 patients were jaundiced and 5 had ascites. Seven had palpable or enlarged livers, and 5 of this latter group had a palpable spleen.

Nine patients in this group had major complicating diseases. Five received antibiotics preoperatively, and 8 during the postoperative period.

Six patients in Group II died of liver insufficiency (Table 1). Death was due to exsanguinating hemorrhage in 2 instances, to cardiovascular disease in one, and to a vascular accident in one. In one case the immediate cause of death was unknown.

Group III. The diagnosis of cirrhosis was made preoperatively in 24 of the 32 surviving patients. It should be pointed out that 13 patients in this group were known to have portal hypertension; 9 of these had a portacaval shunt, and 4 a splenorenal shunt. In 3 patients the cirrhosis was secondary to obstruction in the biliary tract, or followed operations on the gallbladder and bile ducts. Eleven patients in Group III had a past history of jaundice, and 9 of ascites; 3 patients had both. Nine patients had clinical jaundice and 5 had demonstrable ascites at the time of operation. Twenty-one patients had enlarged livers, and splenomegaly was noted in 16. Eleven of the patients with splenomegaly were in the group of 13 who had known portal hypertension secondary to intrahepatic obstruction. The two remaining patients with portal hypertension had had previous splenectomies.

Twenty-one of the 32 patients had other major complicating diseases, and several patients had as many as three major disorders.

The operative procedures are noted in table 2. It will be seen that several patients had more than one operation. The 32 patients in this group had a total of 50 surgical procedures requiring general anesthesia.

Morphine was given preoperatively to 12 patients. Antibiotics were given to 11 patients preoperatively and to 27 postoperatively.

Summary of Medications and Anesthesia

Except in 5 instances, where cyclopropane was used alone in 2, ether in 2, and Pentothal in 1, the anesthestic agents were given in combinations. One of the patients who received only ether during a one hour abdominal exploration expired within the 30 day postoper-

TABLE 1

Group	*Number Cases*	*Cirrhosis Recognized Preoperatively*	*Complicating Diseases*	*Preoperative Diagnoses*	*Causes of Death*
I	9	5	Ulcerative colitis (1) Hypersplenism (1) Hemolytic anemia (1) Nephritis (1) Obstructed duodenal ulcer (1) Heart disease (1)	Cirrhosis, hypersplenism (1) Ulcerative colitis (1) Subphrenic abscess (1) Obstructed duodenal ulcer (1) Bleeding duodenal ulcer (1) Cancer pancreas (1) Xanthomatous disease (1) Cirrhosis, portal hypertension (2)	Coma (8) Coma and hemorrhage (1)
II	11	2	Diabetes (1) Heart disease (1) Hypertension (1) Cancer bladder (1) Cancer prostate (1) Syphilis (1) Hemochromatosis (1) Drug addict, pneumonia (2)	Cancer (3) Biliary obstruction (2) Cholelithiasis (3) Prostatism (1) Cirrhosis, elective surgery (2)	Coma (6) Hemorrhage (2) Cerebrovascular accident (1) Cardiac failure (1) Unknown (1)
III	32	24	Cholelithiasis (7) Peptic ulcer (3) Heart disease (4) Renal stones (2) Syphilis (2) Epilepsy (1) Diabetes (2)	Portal hypertension (13) Cholelithiasis (6) Obstructive jaundice (2) Peptic ulcer (1) Therapeutic abortion (1) Hydronephrosis (1) Renal stones (1) Hernia (2) Cancer (1) Prostatic obstruction (1) Varicose veins (1) Bleeding fibroid (1) Xanthomatous disease (1)	All patients in this group still living after an average follow-up period of 39.1 months.

TABLE 2

OPERATIVE PROCEDURES

Group I (9 Patients)		*Group II (11 Patients)*		*Group III (32 Patients)*	
Exploratory laparotomy, liver biopsy	5	Exploratory laparotomy, liver biopsy	6	Portacaval shunt	6
Gastroenterostomy, liver biopsy	1	Cholecystectomy	3	Cholecystectomy	5
Splenorenal shunt	1	with appendectomy (1)		Herniorrhaphy	5
Portavacal shunt	1	with liver biopsy (1)		Biliary duct surgery	4
Splenectomy	1	Gastrectomy, liver biopsy	1	Splenorenal shunt	4
		Hysterectomy	1	Exploratory laparotomy, liver biopsy	2
		Herniorrhaphy	1	Choledochostomy	2
		Prostatic resection	1	Vein ligation	2
				Nephrectomy	2
				Gastrectomy	2
				Cystoscopy	1
				Exploration	1
				Nephrolithotomy	1
				Sympathectomy	1
				Hysterectomy	1
				Dilatation and curettage	1
				Prostatic resection	1
				Resection of colon	1
Total number at operations	9		13		50

ative period. Cyclopropane was the principal anesthetic employed in 29 cases. Next in frequency were combinations of Sodium Pentothal, ether, and spinal anesthesia. Other anesthetic agents used were ethylene, nitrous oxide, and Surital.

Antibiotics were administered to 29 patients preoperatively and to 41 postoperatively. The antibiotic most frequently employed was penicillin, alone (13 patients) or in combination with other agents (25 patients). Streptomycin alone was given to 3 patients, and Aureomycin to 2. Penicillin and streptomycin in combination were given in 16 cases.

Eleven of 31 patients known to have cirrhosis were given morphine preoperatively.

Analysis of Physical Findings and Laboratory Data

The frequency of ascites varied among the three groups. The difference in the number of patients who had ascites at the time of operation is statistically significant when Groups I and III are compared. The incidence of palpable or enlarged livers was considerably higher in Group III. A comparison with the incidence in Group I revealed the difference to be of probable significance. Palpable or enlarged spleens were found frequently in all groups, and did not appear to be of prognostic significance.

Analysis of the laboratory data also showed significant differences between Groups I and III in the values for hemoglobin, total serum proteins and serum albumin, and in the number of patients with elevated serum bilirubins or prolonged prothrombin times. The frequency of abnormal prothrombin times in Group I was particularly significant in comparison with Group III (Tables 3 and 4).

Liver function tests.

Since some of the patients were operated upon elsewhere and since the diagnosis of liver disease was made preoperatively in only 31 of 52 patients, adequate studies of liver function were not performed in all cases. Where such data were obtained, however, the results are of interest (Tables 3 and 4).

Group I. Eight of the 9 patients who expired within one month after operation were jaundiced at the time of operation, and the average value of the Van den Bergh test in these 8 patients was 3.8 mg. per 100 cc. Determinations of the serum protein, albumin and globulin were obtained in 7 of the 9 patients in this group and were below normal limits in 6. Six patients were found to have a marked anemia; the average hemoglobin value for the entire group was 8.9 Gm. The prothrombin time was abnormally prolonged in 3 of the 6 patients on whom the test was done. In those patients on whom liver function tests were performed, the results obtained were almost universally indicative of extensive and severe liver cell damage.

Group II. In the 11 patients who lived one month to two years following operation

TABLE 3

SUMMARY OF LABORATORY DATA

Test	Normal Range	Group I Done	Group I Abnormal	Group I Average	Group II Done	Group II Abnormal	Group II Average	Group III Done	Group III Abnormal	Group III Average
Total serum proteins	6.3-8.3 Gm.%	7	5	5.8 Gm.%	5	3	5.9 Gm.%	37	12	6.4
Albumin	3.6-5.6 Gm.%	7	6	2.7 Gm.%	4	4	3 Gm.%	33	15	3.55
Cephalin flocculation	0-2 in 48 hours	3	3		4	3		18	15	
Thymol turbidity	0.5 units	1	1	15 units	5	5	23.4 units	19	6	4.7
Alkaline phosphatase	0.5 B.U.*	4	3	8.1 B.U.*	2	0	4.8 B.U.*	15	10	12.2 B.U.*
Van den Bergh	1 mg.% or less	8	8	3.8 mg.%	5	3	2.4 mg.%	26	17	2.2 mg.%
**Bromsulfalein retention	0-5%				3	3	34%	17	15	22.1%
Prothrombin time	25% elevation	6	3		6	0		29	1	
Hemoglobin	11.5 Gm.	8	6	8.9	8	4	12 Gm.	38	13	11.9 Gm.

*Bodansky units

**Done only in patients without jaundice

the total serum protein levels were also decreased, although to a lesser extent than in Group I. Although hemoglobin levels as low as 9.6 Gm. were found in 4 patients, the average for the group was 12 Gm. The prothrombin time was normal in 6 patients on whom the test was performed. The Van den Bergh test showed the serum bilirubin to be elevated in 3 of 5 patients on whom the determination was made. Bromsulfalein retention, averaging 34 per cent in 45 minutes, was found in the 3 patients tested. Liver function tests also showed marked abnormalities in those patients studied.

Group III. Seventeen of the 32 patients still living after an average of 39 months following operation had biochemical evidence of jaundice at the time of operation. Thirty-three determinations of serum albumin were done in 29 patients; 15 were below 3.5 Gm. per 100 cc., and the average for the entire group was 3.55 Gm. per 100 cc. Anemia was noted in 13 patients; the lowest recorded hemoglobin was 8.2 Gm., the mean for the entire group 11.9 Gm. The prothrombin time was determined in 29 patients, and was abnormal in only one instance. The cephalin flocculation test was abnormal in 15 of the 18 patients on whom the test was done. The alkaline phosphatase level was elevated in 10 patients probably as a result of damage to the biliary ducts in most instances.

The Value of Liver Function Studies

The failure to recognize the presence of cirrhosis preoperatively in such a high percentage of these patients serves to illustrate the marked latency of liver disease prior to the onset of clinical manifestations, as well as the difficulty of distinguishing it from other disorders which cause jaundice, ascites, and hemorrhage. Because the liver has such remarkable powers of regeneration, it is often difficult to recognize the presence of functional insufficiency until extensive damage has occurred. The high incidence of abnormal

TABLE 4

COMPARISON OF LABORATORY DATA AND CLINICAL FINDINGS IN GROUPS I AND III

Laboratory Data

Test	Number Tests I	Number Tests III	Mean I	Mean III	Range I	Range III	x^2	Probability	
Albumin (Gm./100 cc.)	7	33	2.7	3.55	2.0- 3.6	1.8- 4.9	3.75	0.1	0.05
Hemoglobin (Gm./100 cc.)	8	38	10.5	11.9	9.6-14.5	8.2-16.7	2.11	0.20	0.10
Prothrombin time	6	29	3 abnormal*	1 abnormal*			10.64	0.01	0.001
Van den Bergh (mg./100 cc.)	8	26					3.76	0.10	0.05

Clinical Findings

	Group I	Group III	x^2	Probability	
Ascites	9	5	22.24	0.001	
Hepatic enlargement	3	21	3.02	0.1	0.05
Splenic enlargement	5	16	0.014	0.9	

*Elevated 25% over standard normal

findings in those patients subjected to liver function tests indicates that the routine performance of such tests prior to surgical procedures will detect many more cases. The importance of accurate preoperative diagnosis is obvious when the mortality rates in the various groups are compared.

It should be emphasized that liver disease is often far advanced before abnormalities of function can be detected by routine laboratory procedures. While the tests of liver function ordinarily utilized measure only a few of the numerous vital functions and do not indicate specifically the type of liver damage, they do denote changes in function and the presence of inflammatory or degenerative parenchymal change. If interpreted in the light of other findings and repeated where necessary, they can be of tremendous diagnostic and prognostic value.

In general, the cephalin flocculation test and determination of the bromsulfalein excretion serve as valuable screening procedures for detecting parenchymal damage in nonjaundiced patients. While these tests uniformly revealed evidence of moderate to advanced functional impairment in the patients of the present series, the findings did not correlate well with the ultimate prognosis. Of greater importance are those procedures which test more primitive and elemental functions of the liver, such as the ability to synthesize albumin and the capacity of the liver to convert vitamin K to prothrombin.

The causal relationship between ascites and low serum albumin levels has been noted by numerous investigators. The finding of low values for serum albumin in patients with cirrhosis not only indicates a decrease in blood proteins, but also provides evidence that labile albumin stores in the extravascular spaces have been depleted as well.[3] Since the amount of albumin in the blood affects the functions of organs and the distribution of fluids among tissues and organs, the inability of the liver cells to form this fraction in adequate amounts is of serious import. In cirrhotic patients this fundamental defect is often further aggravated by blood loss and paracentesis.

Tissue assays reveal that little vitamin K can be stored. Hence, the time required for depletion of the body stores of this vitamin may be only a matter of days. Where hepatic function is unimpaired, vitamin K is transformed rapidly into prothrombin by the liver. Primary parenchymatous disease of the liver diminishes both synthesis and storage of prothrombin. Unless parenchymal involvement is extensive and severe, however, levels are usually adequately maintained. The ability of the jaundiced patient with hypoprothrombinemia to respond to parenteral vitamin K is a valuable measure of hepatic function. Where the liver fails to respond, treatment of the hepatitis is necessary. When such therapy is successful, the production of prothrombin is rapidly restored to normal. If this restoration of function does not occur, the prognosis is poor.

Analysis of the data in the present series reveals the lowest levels of serum albumin and the most frequent occurrence of hypoprothrombinemia to be in Group I. The differences between Group I and III in these respects are great enough to be significant. Although liver function tests do not provide a complete and accurate analysis of the functional state of the liver, the findings obviously bear a rough relationship to the degree of variation from normal. As a rule, the demonstration of severe degrees of impairment and of abnormalities in several of the liver functions indicates a poorer prognosis. It should be emphasized, however, that it is not unusual for liver function tests to be essentially the same in patients whose livers appear quite different on histologic examination.

Evaluation of Physical Findings

It is well recognized that clinical signs and symptoms are often unreliable as a guide to the severity of hepatic damage in a given case. The physical findings in a patient with extensive fatty infiltration of the liver which is amenable to treatment may be essentially the same as those in another patient with marked hepatic scarring and nodular regeneration. Some authorities feel that the presence of hepatic or splenic enlargement, jaundice, collateral circulation, and spider angiomas gives no accurate indication as to the degree of liver insufficiency.

We have previously noted that in 25 of 44 patients with enlarged livers and clinical evidence of cirrhosis, histologic examination showed fatty change in the liver.[4] Because of this frequent association of hepatomegaly with

fatty infiltration, an abnormality which is reversible with treatment, the presence of an enlarged liver may be regarded as indicating a more favorable prognosis. In the present study the incidence of hepatomegaly in Group III was 65.6 per cent, as compared with 33.3 per cent in Group I.

The presence of ascites is almost always associated with a poor prognosis. All of the patients who expired within 30 days after operation (Group I) had ascites, and ascites was present in 46.4 per cent of the patients who succumbed within two years. Of the patients still surviving, only 15.6 per cent had ascites at the time of operation.

Factors Affecting the Prognosis in Cirrhotic Patients

While analysis of the physical findings and laboratory data will not provide a completely accurate prognosis in each instance, the most significant and serious findings are those of ascites, prolongation of the prothrombin time, hypoalbuminemia, jaundice, and a small liver. Derangement of liver function tests is next in importance. The prognosis becomes increasingly poor when blood loss and anoxia are superimposed as a result of hemorrhage or surgery.

Anesthesia and opiates.

The liver, as the largest cellular organ in the body, has a high oxygen requirement. For this reason it is particularly vulnerable to injury. It has been demonstrated that most anesthetic agents which produce anoxia will cause alterations in liver function.[5]

The data here presented reveal that changing trends in anesthesia have resulted in the routine use of spinal anesthesia or cyclopropane, even when the presence of cirrhosis is not recognized. Two patients received ether alone and one of those expired within 30 days. It is almost impossible to evaluate the effects of anesthesia *per se*, since other variables such as the magnitude and duration of the operation and circulatory disturbances associated with the loss of blood and electrolytes are involved.

The data do not indicate that the amount of opiate used pre- or postoperatively had any significant effect upon survival, although it is generally accepted that patients with liver disease tolerate morphine and other alkaloids poorly.[6] In spite of this knowledge, 11 or 31 patients in whom the diagnosis of liver disease was made preoperatively received morphine prior to operation as a part of the routine preoperative procedure.

Antibiotics.

The development of fatty infiltration of the liver following the administration of Aureomycin or Terramycin for prolonged periods (one to two months) has been reported.[7] None of the patients in the present series received antibiotics over this period of time. It has also been reported that Aureomycin may exert a favorable influence in certain instances of severe hepatitis, even when coma is present.[8] A review of the cases here reported did not indicate any specific instances where the use of antibiotics produced changes sufficient to be attributed to the drugs alone. Available information appears to indicate that Aureomycin is the antibiotic of choice for the short-term treatment of patients with liver damage, although penicillin or a combination of penicillin and streptomycin continues to be used more frequently.

Portal hypertension.

The prognosis is extremely poor in patients with cirrhosis who have bleeding from esophageal varices. It has been estimated that 50 to 70 per cent of such patients die within one year following the first hemorrhage. Although such statistics are based largely on surveys made prior to the liberal use of blood transfusions and modern dietary and medical treatment, and often include patients who did not have such emergency treatment as balloon tamponade, the uniformly poor outlook in cirrhotic patients who bleed is well recognized. In 75 per cent of such patients the hemorrhage can be directly attributed to esophageal varices. In many patients with known hepatic insufficiency, an untimely death from hemorrhage can be prevented by a portacaval or splenorenal shunt. Accurate preoperative evaluation for such persons is of extreme importance. Where a poor prognosis is manifested by the various physical and laboratory findings already mentioned, a period of medical management would seem indicated. Patients who fail to respond to adequate medical management, including diet, vitamins, correction of fluid and electrolyte imbalance, transfusions when necessary, diuretics, and a low salt intake, will in all probability fail to survive the immediate postoperative period.

Summary and Conclusions

Improved medical management has resulted in a greater number of remissions in patients with severe liver disease. Consequently these patients now live longer, and often develop related or unrelated disorders requiring elective or emergency surgery.

The risk of operation in patients with severe parenchymatous liver involvement is emphasized by numerous articles in the older literature. While this risk is considerably lessened by modern methods of medical and surgical management, the latency of cirrhosis and the large functional reserve of the liver often delay prompt and accurate diagnosis of this condition. As a result, many patients with liver disease are subjected to major surgical procedures without adequate preoperative preparation. The routine use of "screening" liver function tests will detect the majority of such cases. The diseases most frequently confused with cirrhosis are cholelithiasis, malignancies of the pancreas and liver, and bleeding peptic ulcer.

The signs indicating a poor prognosis in cirrhotic patients are ascites, prolongation of the prothrombin time, hypoalbuminemia, and the presence of a small liver. Less important are anemia (if it is corrected by transfusions preoperatively), clinical jaundice, and abnormal liver function tests. Splenomegaly is of no significance. In patients with findings which indicate a poor prognosis a period of medical management is advisable. Patients who fail to respond to such treatment will in all probability fail to survive the immediate postoperative period.

When the above noted findings are absent, patients with cirrhosis usually have no difficulty in tolerating either cyclopropane anesthesia with adequate oxygenation or spinal anesthesia. The routine use of unselected sedatives and opiates before and after operation probably adds to the risk of surgery. The correct choice of antibiotics increases the cirrhotic patient's chances for a satisfactory recovery.

The data presented serve to confirm the increasing experience that selected patients with cirrhosis are not unfavorable surgical risks if the diagnosis is made preoperatively and if adequate precautions are taken before, during, and after operation.

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Another Method of Treatment of Subdeltoid Bursitis*

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In the hands of the authors, Priscoline has been found to be an effective drug in the treatment of subdeltoid bursitis.

A STUDY OF THE LITERATURE on the treatment of subdeltoid bursitis reveals a considerable amount of confusion as to claims of successful therapy. Methods used in the past include: needle irrigation and saline lavage,[1] stellate ganglion block,[2, 3] vitamin A therapy,[4] vitamin B_{12},[5] ultrasonic application,[6] intravenous iron cacodylate,[7] ultraviolet irradiation of the blood,[8] corticotropin,[9] x-ray therapy,[10, 11] local injection of hydrocortisone acetate,[12, 13] adenosine-5-monophosphate,[14, 15] trypsin,[16] local and intravenous novocain and finally, surgical excision of the calcium if any is present. A British author concluded that all cases after ten days of rest and some sedation would gradually show improvement and would be relieved of distressing pain. If these reports may be taken for gospel, then it is indeed difficult to understand the need for yet another form of therapy.

Our series consists of studies made on 37 patients, all of whom must be classified as having had chronic bursitis or an acute exacerbation of a chronic bursitis. All of the patients had been treated previously by most, if not all, of the methods mentioned above. More than half of the group complained of such agonizing pain as to require hospitalization for from three to seven days.

Statistics

There were 5 males, 32 females. The ages varied from 28 to 85 years, most of them being in the 37 to 50 year group. There was a history of bilateral involvement in 12 cases but no one complained of simultaneous pain in both shoulders. The left shoulders were involved more often than the right (20 to 17) despite the fact that 36 of the patients were right handed. Calcification was present in 21 cases, 4 in males, 17 in females. Calcification did not appear to be responsible for any increase in the intensity of the pain. All of the cases gave a history of limitation of motion prior to the acute exacerbation. History of direct trauma was present in only 4 cases. All of the patients in this series were treated by the intravenous injection of from 25 to 75 mg., or from 1 to 3 cc. of Priscoline, given in divided doses either daily or every other day.

Pharmacology

"Priscoline hydrochloride (2-benzylimidazoline hydrochloride) is a powerful peripheral vasodilator possessing adrenolytic, sympatholytic and cholinergic properties, which suggests its use in various forms of vasospasm. It acts both through the autonomic nervous system and locally to produce dilatation of small blood vessels."

"*Side Effects:* In ordinary therapeutic doses, Priscoline rarely causes undesirable reaction, although nausea and epigastric discomfort have been reported in some instances. Vomiting or diarrhea are less frequently encountered. Tachycardia, flushing, slight rise or fall in blood pressure and increased pilomotor activity with tingling or chilliness have also been noted. These symptoms are generally mild and frequently disappear with continued therapy, regardless of increase in dosage."

"Priscoline causes marked stimulation of gastric activity and an increase in the hydrochloric acid content of the stomach. For this

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reason, it should be used with caution in individuals suffering from gastritis or peptic ulcer or those in whom peptic ulcer is suspected."[17]

Use of the oral drug was attempted but the intravenous route was found to be much more effective.

Results were tabulated by listing as excellent, good, and poor. The excellent results were those who were completely free from pain with the arm at rest and who showed no limitation of motion or pain on motion. The good results included those with almost complete relief of pain with the arm at rest. They required no sedatives and there was some limitation of motion. The poor results had an equivocal relief of pain with the arm at rest and had marked limitation of motion.

Method and Analysis

Seven patients had one injection of 25 mg., 18 had two injections of 25 mg. at each period, 12 had three injections for a total of 75 mg.

Thirty-two of the 37 patients had immediate dramatic relief from the severe pain. In 25 of the cases there was dramatic relief after the first injection, but 18 patients were given second injections because of some returning discomfort. Twelve patients required a third injection because of a residual of a moderate amount of pain. Only one required the use of a sedative following the third treatment, despite the fact that the patient admitted that motion was increased and the pain was certainly a great deal less than on her admission. In 5 of the 37 cases acute exacerbations again appeared from within a period of from 8 months to 6 years. Repeated treatment using 25 mg. relieved all of the patients. Seventeen patients were given continual exercises for from 26 to 120 days before a useful range of painless motion was restored. In only one was it necessary to provide sedation to relieve pain during the exercise.

In 19 cases the results may be classified as excellent, in 17 cases as good, and only in one case as poor.

We have not been able to obtain x-ray follow-up studies of our cases in which calcium deposits were noted on the x-rays. One patient, an acute case not included in this series, did show almost complete absorption of the calcium within a period of just a few weeks. We hesitate to draw any inferences or conclusions from this one case.

After we were convinced of the value of the use of intravenous Priscoline in the treatment of the acute exacerbation of chronic subdeltoid bursitis, we were tempted to try the therapy in acute cases. Five individuals were treated recently and we have been very much encouraged by the results. All five obtained dramatic relief from pain and only two required repeated injections of the drug. None of these cases have been included in our study.

Conclusion

Thirty-seven patients with acute exacerbation of chronic subdeltoid bursitis were treated by the intravenous injection of Priscoline in doses of from 25 to 75 mg. In all of these cases treatment had been by many other methods, and the Priscoline was resorted to almost as a measure of desperation. We have been encouraged by the successful results. We do feel that the use of this drug is a relatively safe, simple, and inexpensive way to treat these patients.

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Discussion (Abstract)

Dr. Richard W. Leong, Houston, Tex. I consider it an honor to be invited to discuss the paper on the treatment of subdeltoid bursitis treated by Priscoline, presented by Drs. Frankel and Strider.

I have had no experience in the use of Priscoline in the treatment of subdeltoid bursitis.

In the series of cases presented in this paper, the majority of the cases required only one to two injections for dramatic relief. It is interesting to consider the mode of action through which this drug acts. The authors mentioned that Priscoline is a powerful vasodilator. Could it be that vasodilation produces this benefit by quieting the inflammatory reaction of the bursa and promoting the transport of the metabolic irritants away from that region? If the vasodilatory effect of one injection of Priscoline lasts only several hours, it would not seem plausible that several hours of the vasodilation would be sufficient to produce the benefit mentioned. We are familiar with certain conditions which we call causalgic syndromes. The shoulder-hand syndrome is one of those conditions. There is a neurophysiologic theory that an autonomic disturbance is part of a vicious circle which maintains a state of irritability at the termination of the pain receptors, possibly by altering local metabolites, in that way leading to continuous stimulation or bombardment of the internuncial pool of the spinal cord. When the efferent elements of this circuit, especially the sympathetic fibers, are interrupted, the vicious circle is broken and the attendant pain is abolished. We know that many of the cases of causalgia-like conditions respond to sympathetic blocks. Perhaps Priscoline, having a sympatholytic action, may exert its beneficial action through a chemical sympathetic block, and may thus break up the vicious circle.

The authors stated that Priscoline rarely causes undesirable actions. They called attention to the fact that Priscoline stimulates the production of hydrochloric acid and should be used with caution in patients suffering from gastritis and peptic ulcer. Recently I reviewed a paper by Dr. Donald Rose of Kansas City, Kansas, on "The Conservative Management of the Painful Shoulder," published in the *Southern Medical Journal*, November, 1951. In his paper, Dr. Rose stated: "Because of the known neurovascular changes which accompany pain, Priscoline in 75 mg. doses given intramuscularly daily or every other day injections may be employed." I wrote Dr. Rose for further information. The following is an excerpt from his letter: "With respect to your query regarding our experience with Priscoline, I have not used this drug in the last year or year and one-half because of a near fatal incident which occurred as a result of the procedure. The more or less synergistic effect between alcohol and Priscoline was not known to me, although I have since learned it to be fairly common knowledge. In one of our patients, who was experiencing severe pain in the shoulder, we gave him 75 mg. of Priscoline intramuscularly, permitting him to rest for a brief period of time before leaving. He apparently left this department and migrated to the nearest tavern where he proceeded to take on an indeterminate amount of alcohol. When I saw the patient several hours later, he was practically in ventricular fibrillation with an extremely rapid pulse, exhibited air hunger, was comatose, and appeared in extreme shock. He was given epinephrine immediately and transported to the hospital, where he was there treated with oxygen and other supportive medication. Fortunately, he survived."

Recently I had a patient with a moderately severe shoulder-hand syndrome, which had its onset following a Colles fracture and subsequently aggravated by coronary heart disease. Among the usual physical findings of this condition, the patient had marked pain and tenderness of the subdeltoid bursa. I thought that this patient would be a good case to put on a trial of Priscoline management. I consulted the Medical Service for possible contraindications in the use of this drug. I was advised against the use of this drug because the possible lowering of blood pressure may be dangerous to this patient's diseased heart. I was also informed that it would be unwise to employ this drug in patients with angina pectoris because of the danger of coronary thrombosis.

In view of the hazards of this drug, I feel that Priscoline should be used with caution and in selected cases.

I have enjoyed remarkable success in the use of local injection of hydrocortisone acetate into the subdeltoid bursa in combination with physical measures to improve the range of motion of the shoulder, and personally prefer it as the treatment of choice.

I wish to thank Dr. Frankel and Dr. Strider for the privilege of discussing their paper.

EDITORIALS

GOUTY NEPHROPATHY

Gouty arthritis was one of the diseases recognized by the practitioners of ancient times. A drug at least similar to colchicum was described in the Ebers Papyrus in 1500 B.C. In the fifth century B.C., Hippocrates described podagra. Colchicum had been definitely established as a therapeutic agent by 500 A.D. Thomas Sydenham described his own personal experience with gouty arthritis and differentiated it from other forms of arthritis in the latter part of the seventeenth century. Over a century ago Garrod demonstrated the excessive amounts of uric acid in the blood by placing a thread in the blood of a gouty patient and demonstrating the crystallization of sodium urate on the thread. Aretaeus is said to have described "a scanty, deep yellow, cloudy urine during attacks of gout."

Though this disturbance in purine metabolism, with its classical manifestation of acute arthritis of a great toe in 60 per cent of cases, is not infrequent, it is a disease commonly missed in the remainder of the cases being classified as some other type of arthritis, tenosynovitis or bursitis. Furthermore, there is another facet of the disease not commonly appreciated though it has been known for many years; it is only in recent years that more attention has been directed to "gouty nephritis." Though knowledge of renal involvement in gout is not new, it was considered to be a complication as the result of vascular disease which also was thought to explain the high incidence of hypertension.

Schnitker and Richter,[1] in 1936, reported that in 17 of 55 cases of gout there was impairment of renal function, being of a vascular type in 15 and glomerular in two. Five died a uremic death, and the pathologic findings in 4 revealed a vascular nephritis in 3, the other presenting the picture of glomerular nephritis. It is of interest that of the remaining 38 cases in their group, 16 had albuminuria but no impairment of renal function as based on function tests. In 1949, Talbot[2] called attention to the possibility of renal disease as a manifestation of gout independent of the arthritis and antedating the latter which may be mild. He indicated that renal failure is probably the most important cause of death in the gouty person, especially if death occurs at an earlier age. Furthermore, he emphasized that urate stones may be passed from the urinary tract before any manifestations of gouty arthritis appear, though urate stones *per se* do not make a diagnosis of a disturbance in purine metabolism.

In the last half dozen years a number of papers have appeared touching upon the subject of the gouty nephropathy. These have pointed to the high incidence of renal disease in gouty patients who have died. Others have described the incidence of renal disease in patients suffering from gout as the result of studies showing albuminuria, casts, and azotemia.

Recently, Fineberg and Altschul[3] have illustrated by case reports, the forms nephropathy may take in gout. In the earlier years of the disease the kidneys seem capable of excreting more uric acid and sodium urate than do the kidneys of the normal person, since the gouty person has an overproduction of uric acid. So long as the plasma is being cleared of this metabolite no abnormality appears. However, if the quantity of urate becomes excessive in the blood and glomerular filtrate, precipitation may occur for some as yet unknown factors. Thus, urates are deposited in certain skeletal structures and in the kidney.

These authors describe the primary type of nephropathy as the changes due to the deposit of urate crystals in the renal interstitial tissues and tubules. Such changes stimulate inflammation, degeneration and foreign body reaction. The urate deposits may be along the collecting tubules and may block the tubular lumen leading to necrosis of the epithelium and atrophy of the nephron. The deposits of urate may cause tophi in the pyramids of the kidney. With atrophy and fibrosis impairment of renal function leads to uremia. As has been indicated before urate stones are com-

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mon. In the renal pelvis they may act as a nidus for the formation of calcium stones of the staghorn type.

The secondary nephropathies may be of two kinds according to these authors. The damage of the primary type surely predisposes to hydronephrosis and plyelonephritis which in turn predisposes to calcium stone formation. Furthermore, gout predisposes to vascular disease, which may be manifest in hypertension, coronary disease, cerebral arteriosclerosis and arteriolar nephrosclerosis. This latter lesion was thought in the past to be the major renal complication of gout, and it was recognized that gouty persons might have chronic renal failure and azotemia for years before death in uremia.

Fineberg and Altschul feel rather strongly that gouty nephropathy may well be partially reversible and that the use of probenecid may relieve the kidney of some of the parenchymal deposits of urate. This drug, by blocking the tubular reabsorption of urates, can maintain a negative balance of uric acid and thus, over the months, must gradually deplete the great miscible pool of uric acid shown to exist by the use of tagged uric acid.

Here then is one form of chronic renal disease which may be in part reversible, or at least, if recognized early, be prevented from either its florid development or progression. The clinician should be aware of the possibility of gouty nephropathy even if the flag of podagra is not flying.

TESTS FOR THE PRESENCE OF INFLAMMATION

The dependence on the erythrocyte sedimentation rate (ESR) which has been in common use since the late twenties has been challenged in recent years by the C-reactive protein test. Fischel[1] has made a careful comparison of the advantages and disadvantages of these tests which are used in the daily practice of medicine.

These tests have come to occupy a prominent position in diseases of the rheumatoid group, though in the medical field the changes accompanying myocardial infarction are also considered to be of importance. Abnormalities as revealed by their use are nonspecific insofar as any disease entity is concerned, but must be interpreted only in terms of evidence for an inflammatory process. Such tests becoming positive under observation, or showing a declining degree of positivity can be considered as indicating the development of, or a decreased production of protein fractions in the area of inflammation respectively.

Fischel chose to compare only these two tests though there are known to be some 30 changes in the blood occurring during inflammation. He feels that the Westergren method of doing the sedimentation test is still the most reliable and therefore preferable to modifications which have been proposed by other investigators. Fibrinogen and certain globulins increase rouleaux formation by red cells providing the basis for the ESR. C-reactive protein derived its name from an abnormal protein found in acutely ill patients which precipitated the C polysaccharide of the pneumococcus. A rabbit antiserum to this protein is used for the precipitation test (CRP).

In comparing the two tests Fischel makes the following points. The ESR is a simpler and less expensive test but requires fresh blood. Though it is claimed that the CRP results are more clearcut than those of the ESR, especially in the lesser degrees of abnormality, this alleged advantage is denied by some investigators. The CRP test seems to be the more sensitive in "acute phase" studies. This is shown in acute myocardial infarction in which the CRP shows a change within the first 24 hours, whereas the ESR reveals no change until the second. However, the CRP test may become negative while electrocardiographic changes continue to evolve during which the ESR test remains positive. Another aspect of this fact is shown in rheumatic fever where the ESR may continue to be abnormal though the CRP test has returned to normal. In a "rebound" of rheumatic disease after cessation of anti-inflammatory medication, the CRP test may not become positive or be delayed in its response, suggesting to one author that the abnormal protein may be depleted or need a greater stimulus for its production. Neither test is specific diagnostically, being indicative only of the probable presence of inflammation. It seems likely that the ESR is a reaction to several abnormal globulin fractions or products of inflammation, thereby accounting for its value from a prognostic viewpoint. On the

1. Fischel, E. E.: The Erythrocyte Sedimentation Rate and the C-Reactive Protein Tests, Bull. Rheumatic Dis. 7 (Suppl.):9, 1956.

other hand the CRP points to a single abnormality in the blood which may explain its reversal while the ESR continues to be abnormal. Both tests show a diminution in the degree of reaction or a disappearance altogether upon the exhibition of anti-inflammatory agents such as salicylates or the steroid hormones, again becoming positive upon the cessation of their use and relapse of the disease process.

From this review it would seem that, all things being considered, the CRP offers little advantage over a well done ESR determination, with the possible exception of an earlier reaction with the C-reactive protein in acute disease.

THE WASHINGTON MEETING

The Golden Anniversary Meeting, held in Washington November 12-15, was a fitting climax to a full year of observing the fiftieth anniversary of the Association.

In retrospect, this meeting was really "one in a lifetime." Its scientific excellence, the social atmosphere, and the birthday spirit added up to an impressive four day occasion.

Within those ninety-six hours around the clock, no less than one hundred and four scheduled functions were held on time and on schedule with from fifty to seven hundred people in attendance at each!

The scientific sessions got off to a fine start on Monday—"D. C. Day"—when two large meetings were presented exclusively by Washington physicians. These sessions, with almost capacity audiences, were followed by forty-eight sessions of the Association's Sections. Again, this year, a splendid Geriatrics Symposium was presented Thursday morning under the chairmanship of Dr. Milford O. Rouse of Dallas.

In addition to the above were the meetings of several specialty societies meeting conjointly which added further variety, versatility and interest to the "educational side" of the meeting.

Attendance-wise, the Washington meeting was the largest single meeting in Southern's history in BOTH physician-registration and over-all attendance. The unofficial (card count) was as follows: physicians registered, 3,173; total registration, 5,438! While the number of *physicians* registered at the Baltimore meeting in 1936 (3,212) was greater, the *total* registered attendance was 559 less.

Of course, registration cards do not reflect the total attendance, either at the Washington meeting or at previous meetings. While every effort was made to get everyone registered, we know many did not. In a convention of this size, and with official programs scattered widely in various hotels, hospitals, institutes, etc., we believe that all registered statistics in every category should be extended five per cent. Thus the more probable (actual) attendance would exceed 5,710 people.

In addition to the 3,173 registered physicians, the record shows 969 ladies; 982 nurses, technicians, exhibitors, visitors and guests; and an astounding 314 medical students attended. Registration statistics on the several conjoint specialty societies, the Southern Flying Physicians and the total Woman's Auxiliary figures were not available at press time.

While the meeting properly celebrated "fifty years of service to the physicians of the South," it pointed confidently and clearly to the future. More emphasis is to be placed on the quality and variety of the Scientific Assembly. The project begun this year of paying expenses of outstanding guest speakers (out-of-territory) will be continued. The Geriatrics Symposium in two years has had fine support and broad appeal. It will be continued, either as a separate program or sponsored jointly by two or more of the regular Sections. The Medical Students Representatives Project, initiated so successfully at Washington will certainly be a feature of future meetings.

Actions of the Council, the Executive Committee, the Board of Trustees, the Editorial Board, the Section Officers and other official bodies of the Southern, and under the enthusiastic leadership of President J. P. Culpepper, Jr., all point to perhaps the greatest meeting ever in Miami Beach on November 11-14, 1957.

A complete 12-page story of this Golden Anniversary meeting will appear as a special feature of the January Journal. It will be a capsule record of a meeting of which every officer and member of the Southern can be justifiably proud.

V. O. F.

25 YEARS AGO

The Cause of Obesity*

"About a generation ago, a movement that had for its objective the demonstration that obesity was often attendant on internal disease began to be generally felt. It was pointed out that many of the most obese persons were apparently not large eaters and that when they were observed in the clinic they did not lose the expected amount of weight, even though the physician believed that he was underfeeding these patients.

"About this time, von Noorden demonstrated that the heat production per kilogram of body weight was definitely lower in obese than in normal persons. He took this fact to mean that the adiposity was caused by some serious abnormality of the metabolism. However, in so doing, he completely ignored the law of surface area, . . . that the basal metabolism of obese persons per square meter of their body surface is also normal.

"It is much more difficult to deal with the second argument, that adiposity is caused by endocrine disease. . . . It is first necessary to determine accurately how much weight should be lost under the circumstances. In order to do this it is essential (1) to know how much energy the subject receives in the diet; (2) to have absolute assurance that the subject adheres strictly to the diet, and (3) to obtain the transformation of energy for the whole period. . . .

"My associates and I have conducted our studies of obesity in such a way that we have been able to deal satisfactorily with each of these three problems. We have made observations on only one subject at a time, while he was confined in what is essentially a metabolism cage, so that he received only the food that we cared to give him. The special diet prepared for him was analyzed in our laboratory so that we knew precisely what he was receiving. Finally, it was necessary to measure the total heat production of the subject. We found that this information could be obtained by calculation from the insensible loss of weight.

"With such data at hand, it is a simple matter to calculate how much body tissue is being destroyed and to plot the loss of weight that is caused by the oxidation of this tissue. When now the course of the body weight of an obese subject who is being undernourished is compared with the loss due to destruction of body tissue, one may find that the two do not coincide. The actual weight may not decrease, even though tissue is certainly being destroyed. . . .

"If now the water exchange is also recorded during such a period, it is found that there is a progressive retention of water by the body. . . . A gain of weight may occur while body tissue is being consumed, solely because water is being added to the body; and weight may diminish in the face of overfeeding because a depletion of water is also taking place. . . .

"Studies such as have been outlined in this article have convinced us that there is only one basic cause of obesity—that it is invariably the result of overeating; expressed technically, that the available energy of the diet exceeds the transformation of energy on the part of the individual.

"Why does anyone eat more than he needs? Because the primitive instinct (appetite) is no longer obeyed or because it has been persistently disregarded so long that it has become dulled and notifies its host too late that the bodily needs have been satisfied. . . ."

*Newburgh, L. H.: The Cause of Obesity, J.A.M.A. 97:1659, 1931.

BOOKS RECEIVED

Essential Urology. By Fletcher H. Colby, M.D., Consultant, Massachusetts General Hospital. Third Edition, illustrated, 645 pages. Baltimore: The Williams & Wilkins Company, 1956. Price $8.00.

Tomorrow's Food. By James Rorty and N. Philip Norman, M.D. Revised and enlarged edition, 279 pages. New York: The Devin-Adair Company, 1956. Price $3.95.

The Clinical Psychologist. By William A. Hunt, Ph.D., Professor of Psychology and Chairman of the Department, Northwestern University. 206 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $5.50.

Alcoholism. Edited by George N. Thompson, M. D., Associate Clinical Professor of Neurology and Psychiatry, University of Southern California, School of Medicine. 536 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $9.50.

Sleep. By Marie Carmichael Stopes. 148 pages. New York: Philosophical Library, 1956. Price $3.00.

Head Injuries and Their Management. By Francis Asbury Echlin, M.D., Professor of Clinical Neurosurgery, New York University—Postgraduate Medical School. 117 pages. Philadelphia: J. B. Lippincott Company, 1956. Price $3.00.

Clinical Chemistry Principles and Procedures. By Joseph S. Annino, Clinical Chemist, Massachusetts Memorial Hospital, Boston. 273 pages. Boston: Little, Brown and Company, 1956. Price $7.50.

Common Contagious Diseases. By Philip Moen Stimson, M.D., Professor of Clinical Pediatrics, Cornell University Medical College, and Horace Louis Hodes, M.D., Pediatrician-in-chief and Director of the Department of Pediatrics, Mt. Sinai Hospital and Clinical Professor of Pediatrics, College of Physicians at Columbia University. Fifth Edition, 83 illustrations and 10 plates. 603 pages. Philadelphia: Lea & Febiger, 1956. Price $8.50.

Lectures on the Scientific Basis of Medicine, Volume IV, 1954-55. 397 pages. New York: John de Graff, Inc., 1956. Price $6.50.

Environment and the Deaf Child. By Steven Getz, Ph.D., School Clinical Psychologist, Audiologist, California School for the Deaf, Berkeley. 173 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $3.75.

Observations on Krebiozen in the Management of Cancer. A. C. Ivy, M.D., Distinguished Professor of Physiology and Head of the Department of Clinical Science, University of Illinois, John F. Pick, M.D., Head of Department of Plastic Surgery, Columbus Hospital, Chicago, and W. F. P. Phillips, M.D., Department of General Practice, St. Francis Hospital, Evanston,

Illinois. 102 pages. Chicago: Henry Regnery Company, 1956. Price $2.50.

An Atlas of Anatomy. By J. B. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor of Anatomy in the University of Toronto. Fourth Edition, Baltimore: The Williams and Wilkins Company, 1956. Price $15.00.

Management of Emotional Problems in Medical Practice. Edited by Samuel Liebman, M.D., Clinical Assistant Professor of Psychiatry, University of Illinois College of Medicine. 146 pages. Philadelphia: J. B. Lippincott Company, 1956. Price $5.00.

New Bases of Electrocardiography. By Dometrio Sodi-Pallares, Professor of Cardiovascular Clinics at the National University of Mexico, with Royall M. Calder, M.D., Editor, English Translation, Clinical Professor of Medicine, Graduate School, Baylor University. 720 pages with 520 illustrations. St. Louis: The C. V. Mosby Company, 1956. Price $18.50.

Internal Secretions of the Pancreas. Volume 9 of Ciba Foundation Colloquia on Endocrinology. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. 287 pages with 100 illustrations. Boston: Little, Brown and Company, 1956. Price $7.00.

Ageing in Transient Tissues. Vol. 2 of Ciba Foundation Colloquia on Ageing. Edited by G. E. W. Wolstenholme, and Elaine C. P. Millar. 256 pages, with 96 illustrations. Boston: Little, Brown and Company, 1956. Price $6.75.

Dermatology. By Donald M. Pillsbury, M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine; Walter B. Shelley, M.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine; and Albert M. Kligman, M.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine. 1282 pages, illustrated. Philadelphia: W. B. Saunders Company, 1956. Price $20.00.

SOUTHERN MEDICAL NEWS

ALABAMA

Dr. Lee F. Turlington, Birmingham, recently elected a member of the Board of the Planned Parenthood Federation of America, Inc., attended a meeting of the National Board in New York City on October 18. The Federation is composed of affiliates of Planned Parenthood Leagues of twenty-seven states.

Dr. William H. Riser, Jr., Birmingham, has been appointed Chairman of the Medical Advisory Committee of the Red Cross for 1957. Dr. Riser is professor of medicine and head of the hematology department at the Medical College of Alabama.

ARKANSAS

Dr. Elmer M. Purcell, Little Rock, has joined the staff of the Holt-Krock Clinic in Fort Smith.

Dr. B. N. Saltzman has been elected president of the Mountain Home Chamber of Commerce.

Dr. James H. Sisson has assumed his new duties as chief of pathology at the Veterans Hospital at Fayetteville.

Dr. W. M. Moten has recently become associated with the Cooper Clinic in Fort Smith for the practice of dermatology.

Drs. Robert W. Ross, Clyde D. Rodgers, and Willis E. Brown have recently been elected chairmen in their respective districts of the American College of Obstetricians and Gynecologists.

Dr. John William Barnett, Cedar Rapids, Iowa, has recently been appointed chief of the urology section of the surgical service at the Veterans Administration Hospital in Little Rock.

Dr. Jim Bethel has recently joined the Bauxite Clinic in association with Dr. B. C. Page.

The Arkansas Radiological Society recently elected Dr. Edwin F. Gray, Little Rock, president; Dr. Joseph A. Norton, Little Rock, vice-president; and Dr. Ernest A. Mendelsohn, Fort Smith, secretary-treasurer.

DISTRICT OF COLUMBIA

Dr. A. B. C. Knudson, director of the physical medicine and rehabilitation service of the Veterans Administration in central office at Washington, and chairman of the Section on Physical Medicine and Rehabilitation of the Southern Medical Association, has recently assumed his duties as president of the American Congress of Physical Medicine and Rehabilitation. He is the first VA physiatrist to head this organization.

Dr. Max Houtchens, Washington, has been appointed chief of the Veterans Administration clinical psychology division in central office at Washington.

At a recent meeting of the American Academy of Pediatrics Dr. George Maksim was appointed chairman of the Committee on School Health. He has been reappointed liaison representative of the Academy to the National Education Association.

Dr. Ralph G. Beachley has recently been elected to Ordinary Membership in the British Royal Society of Health. Ordinary Membership is the highest grade of elective membership in the Society.

Dr. Charles Stanley White, Sr., has been made an Honorary Fellow of the International College of Surgeons. Drs. Irvin Feldman, James Peter Murphy and Saul Schwartzbach were elected Qualified Fellows.

Dr. G. Halsey Hunt has assumed his duties as director of the Center for Aging Research in the National Institutes of Health.

Dr. Edgar B. Johnwick has been appointed Medical Officer in Charge of the U. S. Public Health Service Hospital (National Leprosarium), at Carville, Louisiana.

FLORIDA

Dr. Frederick K. Herpel, West Palm Beach, has returned from a trip abroad where he visited various hospitals and clinics. He toured the Scandinavian countries of Denmark, Sweden and Norway.

Dr. George F. Schmitt, Jr., Miami, has recently been appointed to the Medical Advisory Board of the Mayo Foundation; the Pan American Committee of the American Rheumatism Association, and to the Scientific Exhibit Committee of the American Diabetic Association.

Dr. Richard F. Sinnott, Ft. Pierce, has been elected a director of the Chamber of Commerce for that city.

Drs. John A. Mease, Jr., and James F. Spindler, both of Dunedin, recently attended the Eighth International Congress of Radiology held in the Auditorio Nacional at Mexico City.

Dr. James M. Davis, Jacksonville, has been certified a diplomate of the American Board of Thoracic Surgery.

Dr. Herman Glassman, Miami, has visited clinics and various medical centers in England and other countries of Europe.

Dr. A. Lawson Hardie, Jacksonville, has been elected Chief of the Department of General Practice at the Duval Medical Center in Jacksonville.

Governor Collins has reappointed Dr. C. D. Cooksey, Jacksonville, to the District No. 6 Welfare Board.

GEORGIA

Dr. Peter C. Graffagnini, Columbus, and Dr. Richard Torpin, Augusta, were chairman and vice-chairman respectively of the Georgia section for the American College of Obstetricians and Gynecologists at a recent meeting.

Dr. L. G. Neal, Jr., Cleveland, has been elected president for the newly formed White County Chamber of Commerce.

The following appointments to the faculty of the Medical College of Georgia have recently been approved by the Board of Regents of the University System of the State of Georgia. Dr. Erasmus James McCranie, professor in the department of psychiatry; Dr. Jack Warren Banister, assistant professor of medical microbiology and public health; Dr. Bernard William Shore, assistant professor of biochemistry; Dr. William Curtis Pearcy, instructor in the department of anesthesiology; and Dr. Nancy Mitchell Wende, research associate in medical microbiology and public health.

KENTUCKY

Dr. Frank Wight is now associated with Dr. John L. Dixon in radiology and roentgenology at the Owensboro-Davies County Hospital and Our Lady of Mercy Hospital, Owensboro.

Dr. Marian C. Walton, Melber, is now associated with the community-sponsored Melber Clinic in Graves County.

Dr. Daniel K. Bloomfield has become associated with the Wainer Clinic in Providence.

Dr. Paul E. Schneck recently began his duties as director of the bureau of school health at the Kentucky State Health Department.

The Campbell-Kenton Medical Society presented Dr. John Hadley Caldwell, Newport, and Dr. N. A. Jett, Covington, with 50-year service pins at a recent dinner.

Drs. Rudy Vogt and William E. Oldham, both of Louisville, were chairman and vice-chairman respectively of the Kentucky section of the American College of Obstetricians and Gynecologists which met in November.

Dr. Carlisle Morse, Louisville, has been elected Governor for Kentucky, American Diabetes Association, for the third term.

LOUISIANA

Dr. John C. Mackenzie has recently been appointed a fellow in the American College of Preventive Medicine.

The new faculty members which have been appointed at the Tulane University School of Medicine are as follow. Drs. Derrick B. Jelliffe, visiting professor of tropical medicine; Conrado F. Asenjo, visiting professor of biochemistry; Charles Oderr, associate professor of medicine (radiology); Daniel E. Mahaffey and Page W. Acree, assistant professors of surgery; John D. Krafchuk, assistant professor of dermatology; Joseph F. Dingman, assistant professor of medicine (diabetes); Earl Fisher, Jr., assistant professor of ophthalmology; Dighton F. Rowan, Wolfgang W. Henigst and Donald E. Carey, instructors in epidemiology; Robert F. Ryan, M. J. Rathbone, Jr., and William O. Odom, instructors in surgery; Russell C. Hadley and Louis Krust, instructors in plastic surgery; James M. Fujimoto, instructor in pharmacology; William G. Eckert, instructor in pathology; Marvin Hill and Ronald Meadows, instructors in anatomy; Louis Richard, instructor in radiology; Edward L. Rongone, instructor in biochemistry; Frederick R. Braden, Philip J. Drupp and Charles Farris, Jr., instructors in obstetrics and gynecology; and C. Eugene Linke, speech pathologist.

Dr. H. Warner Kloepfer, associate professor of anatomy at the Tulane University School of Medicine, has recently returned from the First International Congress of Human Genetics held in Copenhagen, Denmark. Dr. Kloepfer presented a paper on "Muscular Dystrophy of the Duchenne Type Transmitted as an Autosomal Recessive."

Dr. George E. Burch, professor and chairman of the department of medicine, Tulane University, presented a paper entitled, "Spatial Vectorcardiography in Myocardial Infarction," to the Fourteenth Congress of Internal Medicine of the U.S.S.R. which met in Moscow in October.

The Louisiana Pathology Society recently elected the following officers: Dr. Rudolph J. Muelling, Jr., New Orleans, president; Dr. Ulysses H. Stoer, Shreveport, vice-president; and Dr. Ralph M. Hartwell, New Orleans, secretary-treasurer.

MISSOURI

Dr. Carl F. Vohs, St. Louis, has been presented with a silver tray, appropriately inscribed, by the Board of Trustees of Group Hospital Service in appreciation for his service on the Board from 1938 and on the executive committee for many years.

Dr. Rush E. Castelaw, Kansas City, has recently been honored for his outstanding work by the Fitzsimmons-Battenfeld Post No. 8 of the American Legion.

Drs. James Barrett Brown and Alvin H. Diehr, both of St. Louis, have been awarded Mississippi Valley Medical Society fellowships.

The medical staff of St. Joseph's Hospital, Kirkwood, has recently named Dr. Donald O. Burst president of the staff. Dr. Francis J. Catanzaro was named president-elect and Dr. Charles C. Drace secretary-treasurer.

Dr. Lewis H. Hoyle has been appointed medical director of the Kansas City Regional office of the Department of Health, Education and Welfare.

Dr. Edward M. Cannon has recently been elected president by the medical staff of Deaconess Hospital. Elected to serve with Dr. Cannon are: Dr. Louis P. Kirtz, vice-president and Dr. Birkle Eck was re-elected secretary.

Continued on page 74

BOOK REVIEWS

Surgical Forum

Clinical Congress of the American College of Surgeons, 1954. 851 pages. Philadelphia: W. B. Saunders Company, 1955. Price $10.00.

This fifth in a series of reports on the Forum on Fundamental Surgical Problems is a review of the latest in surgical investigation. It is the only place in which much of this work can be found since it is not a repetition of material which has previously appeared in one of the periodicals.

Under the chairmanship of Dr. Harris B. Shumaker, Jr., the Forum presented reports of studies carried out on Vascular Surgery, Gastrointestinal Disorders and Physiology, Nutrition and Metabolism, Steroids and Cancer, Anesthesiology, and Burns, in addition to several other interesting general problems. While the mass of this volume is concerned with basic investigation, there is much of interest to the clinician and surgeon who is confronted with the problem of keeping in touch with academic medicine. In many instances the physicians who were able to attend the Forum itself will find that there is much presented in print which was missed in the floor presentations and discussion.

Of particular interest are the studies on substitution of various segments of the gut for the gastric pouch after total gastrectomy, and the reports on the role of antibiotics in intestinal obstruction. There are several reports on the cause of acute pancreatitis and the metabolic changes associated with this disturbance.

The section on Steroids and Cancer was held under the direction of Dr. Francis D. Moore. There was presented a remarkable report of a homologous thyroid gland transplant from an infant to a 29 year old woman who had previously had parathyroid tetany and hypothyroidism. Both disorders were relieved after the transplantation. This is but an example of some of the material covered in this volume.

This is primarily a record of the more interesting research being carried out in the various medical centers in this country. It is of interest as such to persons who are carrying on medical investigation and to those who try to maintain some touch with the rapidly changing picture of surgery and surgical physiology.

Cold Injury. Transactions of the Third Conference February 22-25, 1954, Fort Churchill, Manitoba, Canada

Edited by M. Irene Ferrer, M.D., Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, N. Y. 226 pages. New York: Josiah Macy, Jr. Foundation, 1955. Price $4.50.

This is the report of the Third Conference on Cold Injury sponsored by The Josiah Macy, Jr. Foundation and held at Fort Churchill, Manitoba, Canada, in February, 1954. It is the edited, transcribed proceedings of this conference. The nineteen conferees and guests bring to the discussion the variety of viewpoints which one has come to associate with the interdisciplinary technic of the Macy Foundation Conferences.

The discussion is divided into chapters which deal with the interrelationships of circulatory and metabolic factors, metabolic studies of the Eskimo, a comparison of Eskimos with acclimatized white males, studies of fat distribution and metabolism as influenced by environmental temperature, diet and survival, and the role of ascorbic acid and of subcutaneous fat in the prevention of cold injury in man. The book is usefully indexed. This report is not intended to be a guide to treatment or prevention of cold injury. Instead, it is an exchange of information between those actively investigating the subject and informed scientific workers interested in the phenomenon of cold injury. Accordingly, the book is of more immediate interest to the physiologist, nutritionist and clinical investigator than to the practicing physician.

The customary style of reporting the conferences sponsored by this Foundation may meet with criticism by some readers, but this reviewer finds that it provides an insight into the investigational problems and experimental processes of those close to advances in the field. It is a welcome diversion from the all-too-stereotyped review so characteristic of our present-day scientific literature.

INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Footnotes and bibliographies should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

Editorial Address: All manuscripts, corrected galley proof, reprint orders, books for review and related correspondence should be addressed to the Editor, R. H. Kampmeier, M.D., Vanderbilt University School of Medicine, Nashville 5, Tennessee.

Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, Empire Building, Birmingham 3, Alabama.

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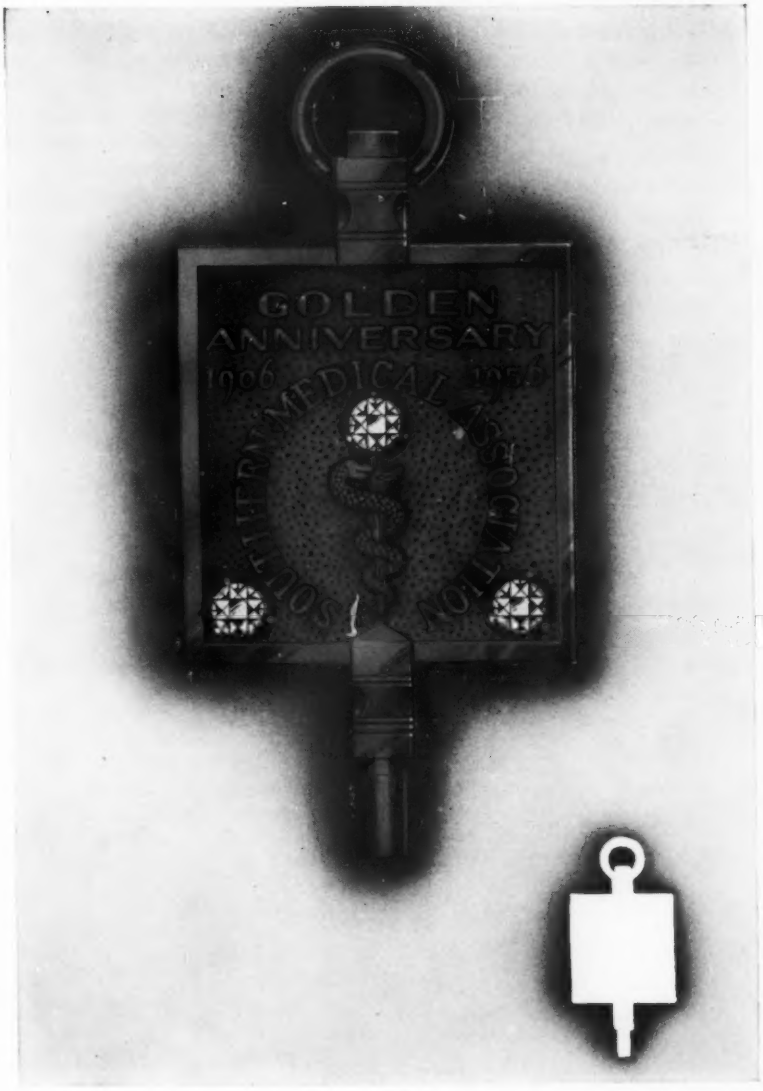

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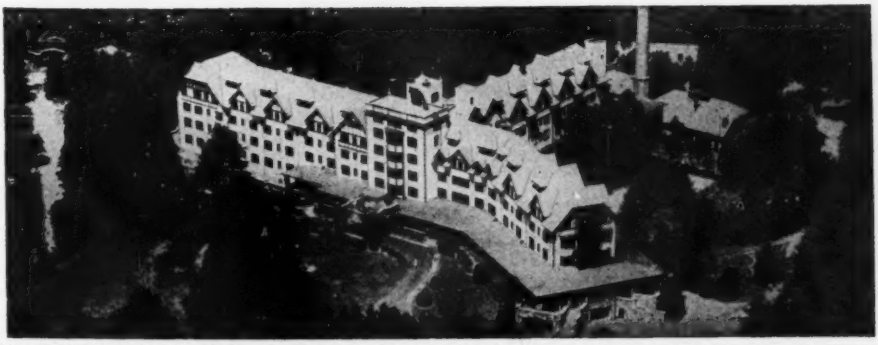

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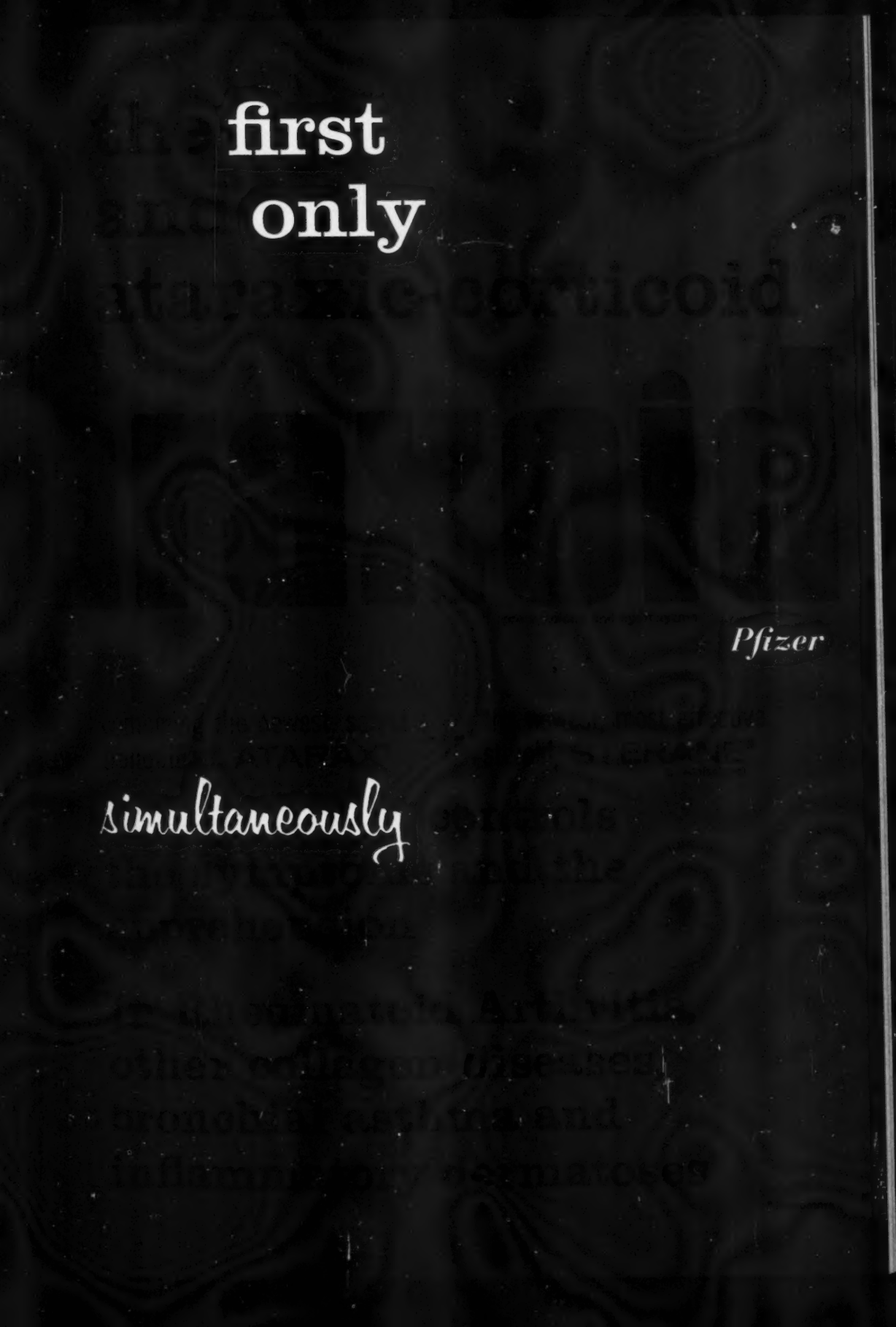

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when blood pressure must drift down . . . not plunge
Nitranitol R.S.
Dosage: In blood pressures over 200 systolic, 2 tablets four times daily. In other cases, 1 or 2 tablets every four to six hours. Supplied: Bottles of 100 and 1,000.
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Continued from Page 1521

Dr. Edward Crites, Sedgewickville, has recently been appointed coroner of Bollinger County by the governor.

Dr. Paul I. Robinson has been appointed executive director of the Civilian Medical Care Program.

Dr. Robert Elman, St. Louis, is a member of the government advisory committee to develop methods of providing improved hospital care at lower cost.

Dr. B. M. Stuart, Boonville, has been appointed to serve as Councilor of the Association from the Fifth Councilor District to fill the unexpired term of Dr. James W. Allee who has moved to Treasure Island, Florida.

Drs. Willis H. Reals, professor of adult education and chairman of the Washington University gerontological committee; William B. Kountz, assistant professor of clinical medicine and president of the Gerontological Society of the United States; and E. V. Cowdry, director of the Wernse Laboratory of Cancer Research, were decorated for their distinguished work in gerontology by the Mexican Academy of Gerontology at the first Pan-American Congress of Gerontology which was held recently in Mexico City.

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WANTED—EENT Associate, fine southern community, lucrative, long established practice. Contact HP c/o SMJ.

LOCATION WANTED—Internist, 35 years of age, married, board certified; VA training, university affiliated; graduate Minnesota; licensed Minnesota, Missouri; previous group practice experience; completing military service; available January 1957; clinic or group association desired; south or southwest. Reply to ZHN c/o SMJ.

NOTICE—Will the resident in Virginia who contacted box GG in care of the Southern Medical Journal regarding a preceptorship kindly do so again.

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WANTED—South Central Florida—General Practitioner to take over office of retired doctor; fully equipped 6-room office, including intact patient records; rent $50.00 per month; for details contact: A. L., 67 N. Ridgewood, Sebring, Florida.

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LOCATION WANTED — General Practitioner, 34 years, would like location in Texas or Oklahoma or would consider other state. Has Texas and Oklahoma license. Can furnish excellent references. Contact AE c/o SMJ.

Dr. Wendell G. Scott, professor of clinical radiology at Washington University, has been elected president-elect of the American Roentgen Ray Society.

Dr. Arthur E. Strauss, assistant professor emeritus of clinical medicine, Washington University, has been named chairman of the 1957 St. Louis Heart Association fund drive.

Dr. Gilbert Ryder has been appointed clinical associate in medicine (dermatology) at the University of Missouri.

Dr. A. A. White, presently assistant professor of biochemistry, Georgetown University, Washington, D. C., will become assistant professor of biochemistry at the University of Missouri on January 1, 1957.

Dr. George F. Reddish, professor of microbiology and public health at St. Louis College of Pharmacy and Allied Sciences, has received the 1956 Achievement Award of the Chemical Specialties Manufacturers' Association for technical contributions in the fields of public health, disinfection, and antisepsis.

NORTH CAROLINA

Newly elected officers of the North Carolina Surgical Association are: Dr. Alexander Webb, Raleigh, president; Dr. Howard Starling, Winston-Salem, president-elect; Dr. John Brabson, Charlotte, vice-president; and Dr. Alfred Hamilton, Raleigh, secretary-treasurer.

At a recent meeting of the North Carolina Chapter of the American Academy of General Practice the following officers were elected: Dr. John Mewborn, Farmville, president; Dr. C. T. Wilkinson, Wake Forest, president-elect; and Dr. Zack Long, Rockingham, vice-president. Directors for a period of three years are: Second District, Dr. D. L. Moore, Greenville; Fifth District, Dr. Ralph Garrison, Hamlet; and Ninth District, Dr. Lloyd Roberson, Salisbury.

The North Carolina Orthopaedic Association Meeting was held on the Duke University Campus, Durham, October 19-20. Those participating in the program were: Drs. W. C. Davison, Deryl Hart, Guy Odom, Nicholas Georgiade, C. R. Stephen, W. C. Sealy, Barnes Woodhall, Keith Grimson, W. W. Shingleton, E. P. Alyea, Norman Conant, E. L. Persons, James Wyngaarden, J. Leonard Goldner, J. E. Markee, Robert Brashear, and John Baluss. Officers for this Association are: Dr. E. I. Bugg, Jr., president and Dr. J. Leonard Goldner, secretary.

Dr. Robert J. Reeves, chairman of Duke Medical School's radiology and x-ray technology departments, has been honored by former students and associates at a special alumni gathering.

Dr. Charles L. Johnston, Jr., has joined the staff of the department of physiology of the University of North Carolina School of Medicine.

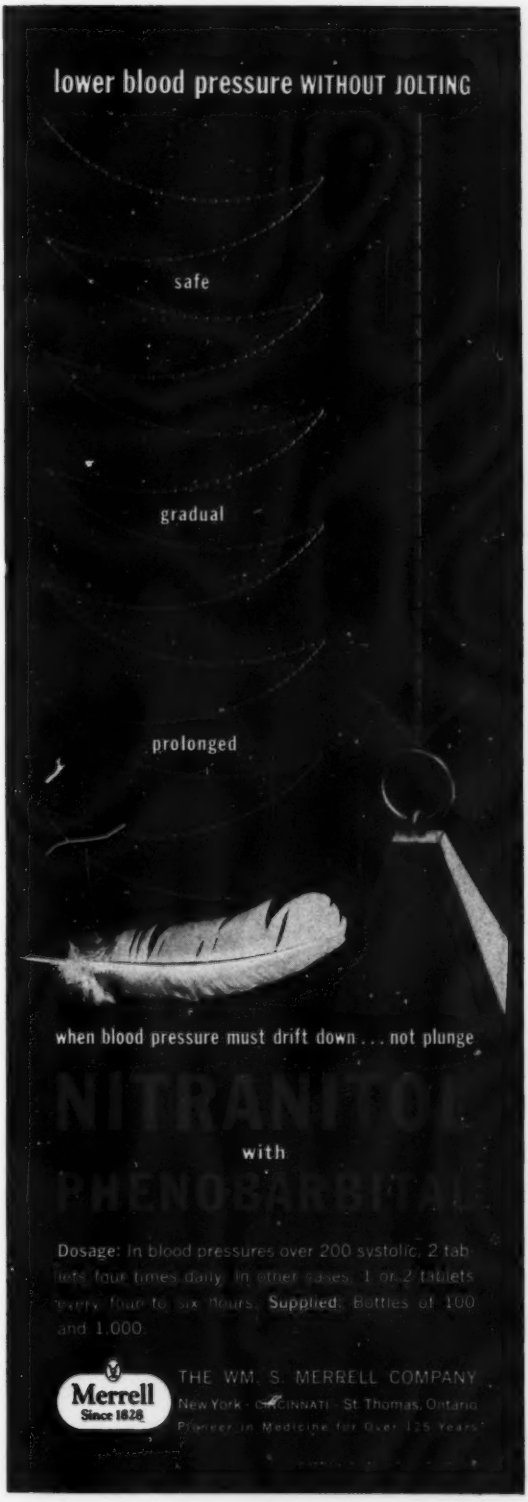
OKLAHOMA

Dr. Reece R. Boone, Jr., is the new chief surgeon at the Northwest Community Hospital in Mooreland.

Dr. Leonard P. Eliel has been named acting director of the Oklahoma Medical Research Foundation.

Dr. James Mitchell Fite has taken over duties in

Continued on page 84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of

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Conference Headquarters—Municipal Auditorium

March 11, 12, 13, 14, 1957

GUEST SPEAKERS

Emery A. Rovenstein, M.D., New York, N. Y.
Anesthesiology

Nelson Paul Anderson, M.D., Los Angeles, Calif.
Dermatology

J. Edward Berk, M.D., Detroit, Mich.
Gastroenterology

Erle Henriksen, M.D., Los Angeles, Calif.
Gynecology

Ovid O. Meyer, M.D., Madison, Wis.
Internal Medicine

Irvine H. Page, M.D., Cleveland, Ohio
Internal Medicine

Barnes Woodhall, M.D., Durham, N. C.
Neurosurgery

John E. Savage, M.D., Baltimore, Md.
Obstetrics

C. Dwight Townes, M.D., Louisville, Ky.
Ophthalmology

Don King, M.D., San Francisco, Calif.
Orthopedic Surgery

G. Slaughter Fitz-Hugh, M.D., Charlottesville, Va.
Otolaryngology

Malcolm B. Dockerty, M.D., Rochester, Minn.
Pathology

Sydney S. Gellis, M.D., Boston, Mass.
Pediatrics

Karl Zimmerman, M.D., Pittsburgh, Penna.
Proctology

Laurence L. Robbins, M.D., Boston, Mass.
Radiology

Danely P. Slaughter, M.D., Chicago, Ill.
Surgery

C. Stuart Welch, M.D., Albany, N. Y.
Surgery

William L. Valk, M.D., Kansas City, Kan.
Urology

Lectures, symposia, clinicopathologic conferences, round-table luncheons, medical motion pictures, scientific exhibits and technical exhibits.

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Demerol® hydrochloride	30 mg. (½ grain)

Average Adult Dose... 1 or 2 tablets repeated in three or four hours as needed.

○ ***marked potentiation of analgesia***

plus ..... *mild sedation*
..... *antispasmodic action*
..... *antipyretic action*
..... *no constipation*
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"Such a combination has proved clinically to be far more effective and no more toxic than equivalent doses of any of these used singly."

Bonica, J.J.; and Backup, P.H. (Tacoma General Hospital, Washington): *Northwest Med.*, 54:22, Jan., 1955.

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At last! a nutritive deconstipant

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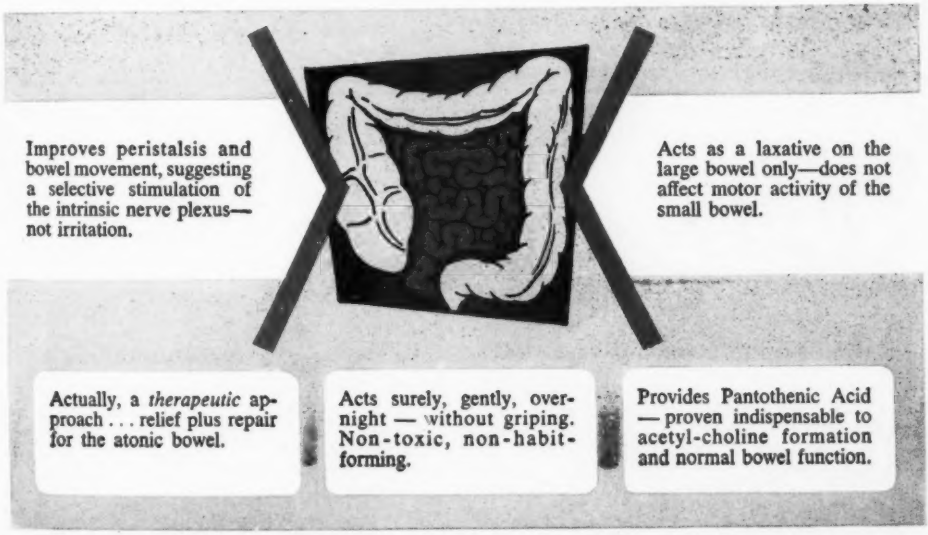
which not only relieves but also rehabilitates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Continued from page 75

obstetrics and gynecology at the Fite Clinic in Muskogee.

Dr. Robert E. Herndon has been certified by the American Board of Pediatrics.

Dr. J. E. Hollis, Bristow, has been named chief of staff of the Bristow Memorial Hospital.

Dr. Patrick Shanks, Enid, has been awarded a fellowship in the American Academy of Obstetrics and Gynecology.

Recently elected officers of the Oklahoma State Radiological Association are: Dr. Lucien M. Pascucci, Tulsa, president; Dr. Simon Pollack, Tulsa, vice-president; and Dr. Sol Wilner, Tulsa, secretary-treasurer.

SOUTH CAROLINA

Dr. Boris Gertz, formerly of Florida, has been appointed to the psychology staff of the State Hospital.

Dr. Z. Agardy has become an assistant physician at the South Carolina State Hospital.

Dr. William C. Cantey, Columbia, has been appointed surgical consultant by the Surgeon-General of the U. S. Army.

Dr. J. O. Beasley, Jr., Charleston, is now surgeon in charge of the U. S. Public Health Service outpatient clinic.

Dr. Wallis Cone, Williston, has been recently elected chief-of-staff at the Barnwell County Hospital. Dr. E. R. Wallace III, Barnwell, assistant chief-of-staff and Dr. L. W. Anderson, Williston, chief of surgery.

Dr. Joe E. Freed has been elected president of the South Carolina State Employees Association and Dr. John M. Preston was elected vice-president.

Dr. Purves James Boatwright recently assumed his duties as assistant physician at the South Carolina State Hospital in Columbia.

Dr. James R. Reid, Jr., has been assigned as Commanding Officer of the U. S. Naval Hospital in Beaufort.

Dr. A. L. Allen has been serving as Consultant in Radiology to the National University of Taiwan, School of Medicine, Taipei, Formosa, China.

The Alumni Association of the University of South Carolina has elected Dr. W. S. Brokington, Greenwood, president.

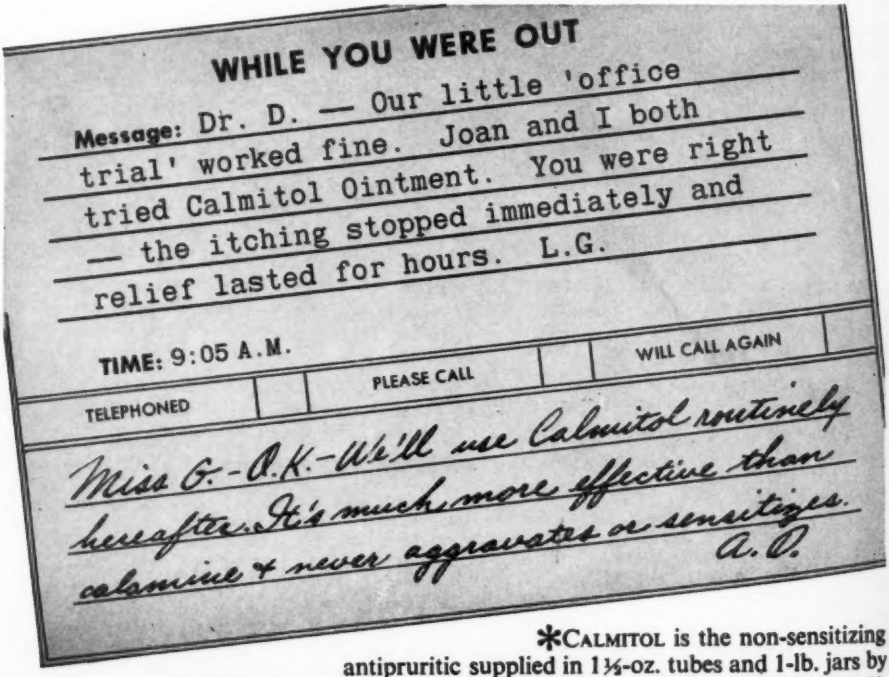
Dr. J. R. Sosnowski has been made a Diplomate of the American Board of Obstetrics and Gynecology.

Dr. Kenneth W. Kruger has recently been made a member of the American College of Physicians.

The Industrial Medical Society of South Carolina recently elected the following officers: Dr. Frank Owens, Columbia, president; Dr. J. L. Hughes, Greer, president-elect; Dr. J. T. Assey, Georgetown, vice-president; Dr. C. B. Hanna, Spartanburg, secretary; and Dr. F. H. Stelling, Greenville, treasurer.

The newly elected officers of the South Carolina Academy of General Practice are: Dr. C. N. Wyatt, Greenville, president; Dr. H. M. Eargle, Orangeburg, president-elect; Dr. I. R. Wilson, Charleston, vice-

Continued on page 89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Miss G. - O.K. - We'll use Calmitol routinely hereafter. It's much more effective than calamine & never aggravates or sensitizes.
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Publication 234

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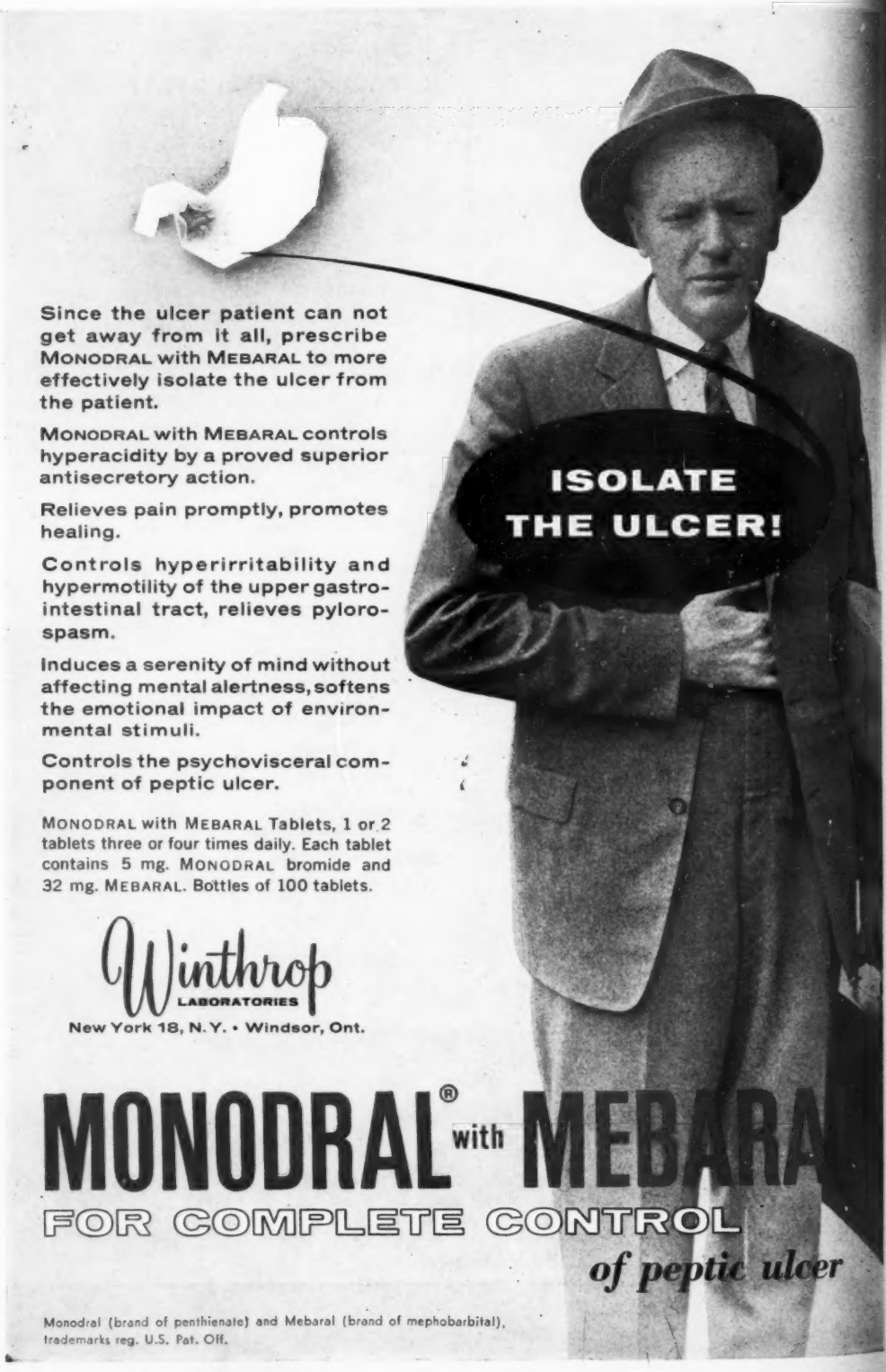

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(1) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956. (2) Amols, W.: J.A.M.A. 160:742 (Mar. 3) 1956. (3) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956. (4) Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

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KARNAKY reports in treating vaginal trichomoniasis ". . . approximately 39 to 47 percent of resistant cases are reinfections from the sexual partner."[1]

Symptom-free carriers. Most infected husbands of infected wives are asymptomatic. They are ". . . none the less a potential source of reinfection in wives successfully treated."[2]

Protect the wife. Karnaky recommends in recurrent cases of vaginal trichomoniasis that the husband wear a prophylactic at coitus for as long as four to nine months. By the end of this time the trichomonads he harbors will usually die out.[3]

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References: 1. Karnaky, K. J.: Urol. & Cutan. Rev. 42:812 (Nov.) 1938. 2. Lanceley, F., and McEntegart, M. G.: Lancet 1:668 (Apr. 4) 1953. 3. Karnaky, K. J.: J.A.M.A. 155:876 (June 26) 1954. 4. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955.

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A two months full-time course. In Obstetrics: lectures, prenatal clinics; attending normal and operative deliveries; detailed instruction in operative obstetrics (manikin). X-ray diagnosis in obstetrics and gynecology. Care of the newborn. In Gynecology: lectures; touch clinics; witnessing operations; examination of patients pre-operatively; follow-up in wards post-operatively. Obstetrical and gynecological pathology. Culdoscopy. Studies in sterility. Anesthesiology. Attendance at conferences in obstetrics and gynecology. Operative gynecology on the cadaver.

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A two months combined course comprising attendance at clinics and lectures; instruction in examination, diagnosis and treatment; pathology, radiology, anatomy, operative proctology on the cadaver, anesthesiology, witnessing operations, examination of patients pre-operatively and post-operatively in the wards and clinics; attendance at departmental and general conferences.

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Continued from page 84

president; Dr. H. M. Whitworth, Greenville, secretary-treasurer; and Dr. J. H. Cutchin, Easley, new director on the three-member directorate.

TENNESSEE

Dr. Grant W. Liddle has joined the Vanderbilt University School of Medicine, Department of Medicine, as associate professor.

Dr. F. Tremaine Billings, Nashville, has been elected to the Board of Trust of Princeton University.

The National Flying Physicians Association has recently elected Dr. S. B. Sullenberger, Dandridge, president.

The Henry County General Hospital has elected Dr. R. G. Fish, Paris, chief-of-staff; Dr. Horace McSwain, vice-chief; Dr. John E. Neumann, secretary; and Drs. E. P. Mobley and K. G. Ross, members of the executive committee.

The Brownsville Rotary Club has presented Dr. John C. Thornton, Brownsville, with a plaque in recognition of his 44 years as a doctor in Haywood County.

Dr. Gilbert Eblen, Knoxville, attended the Eighth International Congress of Pediatrics in Denmark.

Dr. Humphrey K. Ezell, formerly of South Carolina, has been appointed senior scientist at the Special Training Division of the Oak Ridge Institute of Nuclear Studies.

Dr. Alvin J. Cummins, assistant professor of medicine at the University of Tennessee, is the author of a section on diseases of the small intestine in the recently published sixth edition of Meakin's "Practice of Medicine." Dr. Cummins also has been appointed to the staff of abstractors of the *Journal of Gastroenterology*.

At a recent meeting of the American Paraplegia Society Dr. B. A. Moeller, Jr., Memphis, was elected secretary.

VIRGINIA

Dr. Rachel Weems is now located at the Woodrow Wilson Rehabilitation Center in Fishersville.

The inauguration of Dr. Robert Blackwell Smith, Jr., as the fourth president of the Medical College of Virginia will take place on December 17 at 11:00 a.m., in The Monumental Church, Richmond. The Chairman of the Board of Visitors of the college, Buford Scott, will preside at this inaugural ceremony. Dr. James Rawlings Sydnor's organ prelude will be *Benedictus* by Alec Rowley. The music for the academic procession will be *Marche Triomphale* by Sigfrid Karg-Klert. Heading the procession, marshaled by Dr. Alton Dean Brashear of the school of dentistry, will be the presidential party. Next in line will be members of

Continued on page 92

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PRECALCIN
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A DIETARY SUPPLEMENT
FOR USE DURING PREGNANCY AND LACTATION
EACH CAPSULE CONTAINS:
CALCIUM LACTATE Anhydrous 450.00 mg
VITAMIN A Crystalline 2,000 U.S.P. Units
VITAMIN D3 Crystalline 400 U.S.P. Units
THIAMINE HCl 3.00 mg
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VITAMIN B12 conc. - activity equiv. to 1.00 mcg
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TRACE ELEMENTS*
* As Added Micronutrients
MICRONUTRIENTS
Copper as Copper Sulfate .2 mg.; Manganese as Manganese Sulfate .2 mg.; Cobalt as Cobalt Sulfate .04 mg.; Zinc as Zinc Oxide .2 mg.; Magnesium as Magnesium Sulfate .2 mg.; Molybdenum as Sodium Molybdate .04 mg.; Iodine as Potassium Iodide .02 mg.; and Fluorine as Calcium Fluoride .84 mg.
DOSE: 1 capsule three times daily, or as prescribed.
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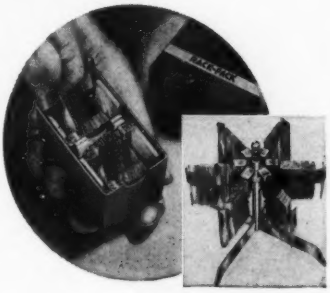

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Continued from page 89

the Board of Visitors, followed by several hundred delegates of colleges, universities, learned societies and organizations from over the nation. The faculty of the college and representatives of the student body will complete the procession of approximately 400.

Dr. William F. Maloney has been appointed dean of the Medical College of Virginia effective January 1, 1957.

WEST VIRGINIA

Dr. E. Lyle Gage, Bluefield, has been elected president of the West Virginia State Medical Association at a recent meeting and will take office on January 1, 1957. To serve with Dr. Gage are: Dr. George F. Evans, Clarksburg, vice-president; and Dr. T. Maxfield Barber, Charleston, was named to his 30th consecutive term as treasurer. Members of the Association elected to serve a two year term on the Council are: First district, Dr. Seigle W. Parks, Fairmont; second, Dr. Charles L. Leonard, Elkins (reelected); third, Dr. L. E. Neal, Clarksburg; fourth, Dr. Ray H. Wharton, Parkersburg (reelected); fifth, Dr. L. J. Pace, Princeton; and sixth, Dr. William L. Cooke, Charleston.

At a recent meeting of the West Virginia Trudeau Society the following officers were elected: Dr. Haven M. Perkins, Charleston, president; Dr. George F. Evans, Clarksburg, vice-president; and Dr. Morris H. O'Dell, Charleston, secretary-treasurer.

Dr. James Howard Anderson, Welch, has been selected as the first recipient of the "General Practitioner of the Year" award which was presented by the State Medical Association.

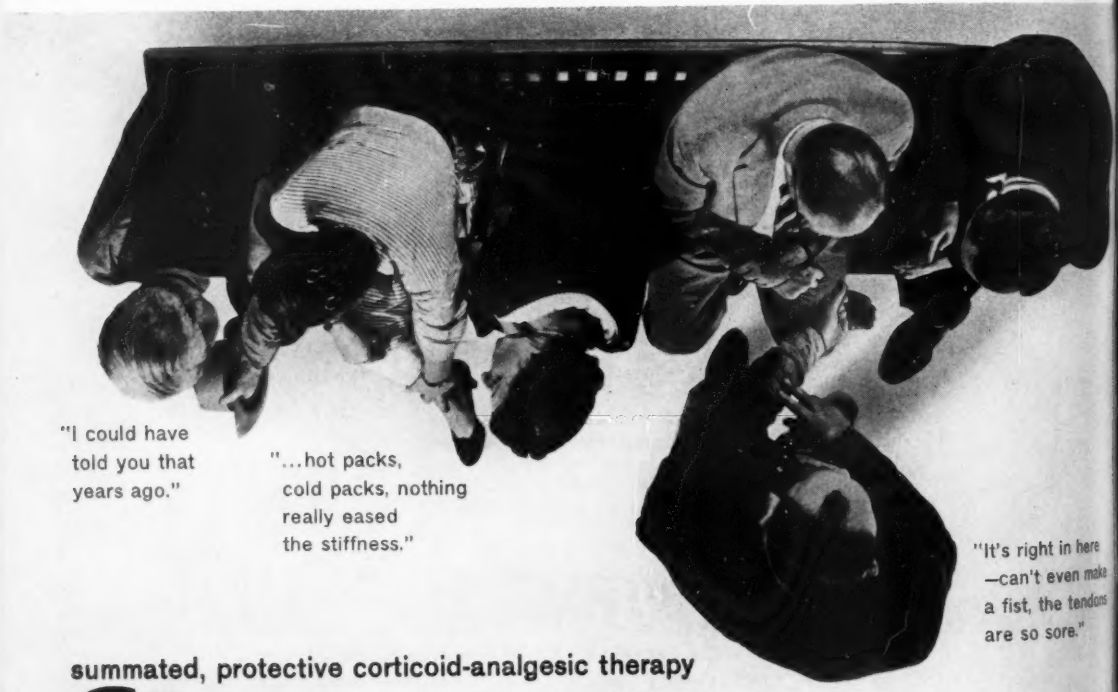
Dr. Rupert W. Powell, Fairmont, has been elected president of the West Virginia Chapter of the Medical College of Virginia Alumni Association.

Dr. Dan N. Barber, Charleston, has recently been elected president of the Alumni Association of West Virginia University School of Medicine. Other officers elected were: Dr. John F. McCuskey, Clarksburg, vice-president; and Dr. Clark K. Sleeth, Morgantown, re-elected secretary-treasurer. Dr. J. Brown, Craigsville, was elected a member of the executive council.

Dr. Joseph T. Mallamo, Fairmont, won the medical golf tournament which was held in connection with the recent annual meeting of the State Medical Association.

Dr. W. H. St. Clair, Jr., Bluefield, has been named chairman of the program committee for the 90th annual meeting of the West Virginia State Medical Association which will be held at the Greenbrier in White Sulphur Springs, August 22-24, 1957.

Dr. Clark K. Sleeth, Morgantown, was recently installed president of the West Virginia Heart Association. Other officers elected to serve with Dr. Sleeth are: Dr. Lynwood D. Zinn, Clarksburg, vice-president; and Dr. James H. Walker, Charleston, secretary.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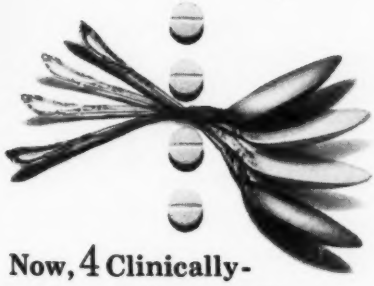

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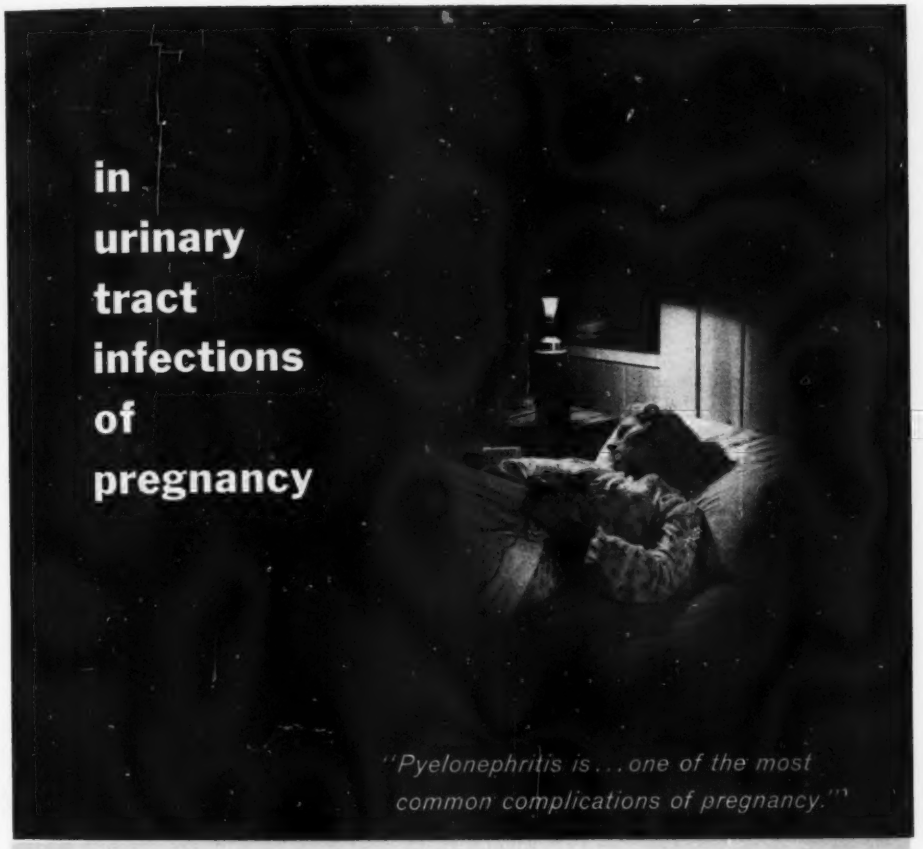

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References: 1. Kass, E. H.: Am. J. Med. 18:764, 1955. 2. Diggs, E. S., Prevost, E. C., and Valderas, J. G.: Am. J. Obst. 71:399, 1956.

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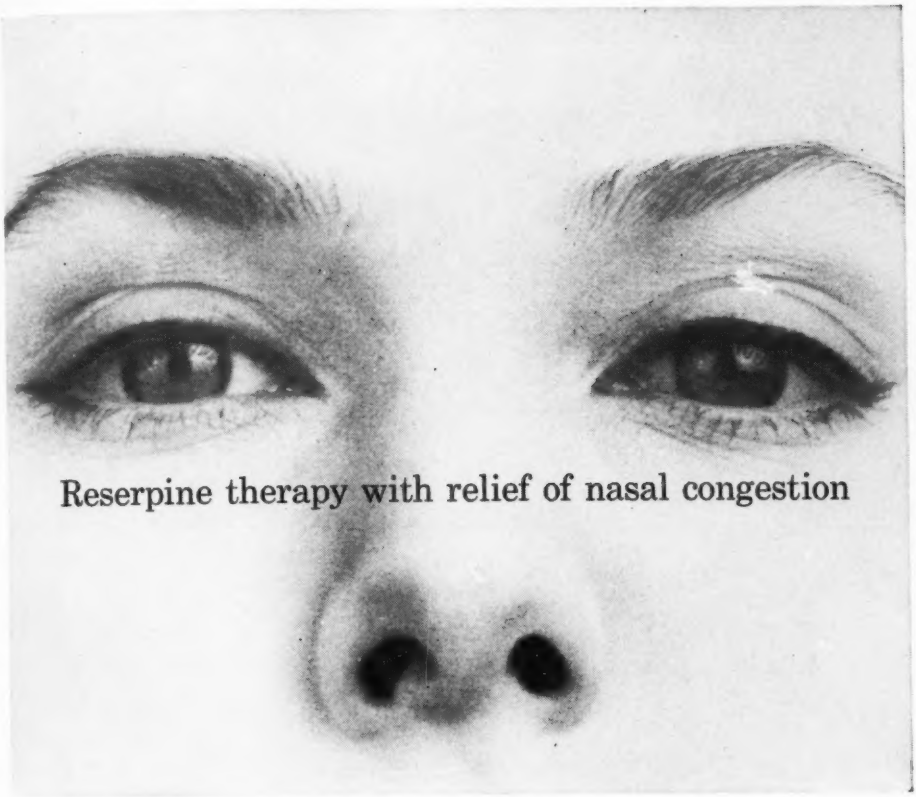

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